DISSERTATION

on

"STUDY ON THE PREVALENCE OF METABOLIC SYNDROME IN THE NEWLY DIAGNOSED HYPOTHYROID PATIENTS

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CERTIFICATE

This is to certify that the dissertation entitled **"STUDY ON THE PREVALENCE OF METABOLIC SYNDROME IN THE NEWLY DIAGNOSED HYPOTHYROID PATIENTS"** is a bonafide work done **by DR. P.MANIVANNAN**, Post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai -03, in partial fulfilment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the academic year 2013 – 2016.

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DECLARATION

I solemnly declare that the dissertation entitled **"STUDY ON THE PREVALENCE OF METABOLIC SYNDROME IN THE NEWLY DIAGNOSED HYPOTHYROID PATIENTS"** is done by me at Madras Medical College, Chennai – 03 during April 2015 to September 2015 under the guidance and supervision of **Prof. Dr. R. PENCHALAIAH**, to be submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfilment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE BRANCH-I

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CONTENTS

LIST OF ABBREVIATIONS

EGIR	-	European Group for the study of Insulin Resistance
NCEP	-	National Cholesterol Education Panel (US)
ATP	-	Adult Treatment Panel
BMI	-	Body Mass Index
DASH	-	Dietary Approaches to Stop Hypertension
ADA	-	American Diabetes Association
PVAT	-	Peri Vascular Adipose Tissue
ASCVD	-	Arterio Sclerotic Cardio Vascular Disease
G6P	-	Glucose 6-Phosphate
NADH	-	Nicotinamide Adenine Dinucleotide Hydride
NAD	-	Nicotinamide Adenine Dinucleotide
PPAR	-	Peroxisome Proliferator-activated Receptor
NO	-	Nitric oxide
MCP	-	Monocyte Chemoattrantant Protein
cAMP	-	cyclic Adenosine Mono Phosphate
ET	-	Endothelin
RAS	-	Renin Angiotensin System
TNF	-	Tumour Necrosis Factor
PCOS	-	PolyCystic Ovarian Syndrome
FFA	-	Free Fatty Acid

TGS	-	Triglycerides
VLDL	-	Very Low Density Lipoprotein
HDL	-	High Density Lipoprotein
LDL	-	Low Density Lipoprotein
CKD	-	Chronic Kidney Disease
CHD	-	Coronary Heart Disease
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance
OGTT	-	Oral Glucose Tolerance Test
ACE	-	Angiotensin Converting Enzyme

ABSTRACT

STUDY:

Study on the Prevalence of Metabolic syndrome in the Newly diagnosed Hypothyroid Patients.

BACKGROUND

Metabolic Syndrome is common cause of Cardiovascular morbidity and mortality which is commonly associated with hypothyroidism Identification of metabolic syndrome in Hypothyroidism aids in early interventions.

MATERIALS AND METHODS

This study included 100 members with 50 in Study group (Hypothyroid) and 50 in control group (Euthyroid) The screening for metabolic syndrome in study and control group is based on IDF criteria. 15 among study group and 6 among control group had metabolic syndrome with significant p value < 0.05.

Among Lipid Profile Parameters Total Cholesterol, LDL, TG increased, and HDL decreased in study group compared to control group with significant P value < 0.05.

RESULT

Metabolic syndrome is common in Hypothyroid than Euthyroid. Lipid profile parameters also had independent correlation with hypothyroidism. LDL, Total cholesterol, TG increased and HDL decreased in Hypothyroidism than Euthyroid state.

KEYWORDS:

Metabolic syndrome, hypothyroidism, Euthyroidism, IDF Criteria, lipid profile, obesity Insulin resistance, Hypertension, CVD.

INTRODUCTION

- Hypothyroidism is one of the most common endocrine disorders in the developing world

- Hypothyroidism is a recognized risk factors for atherosclerotic cardiovascular disease, hyperlipidemia, low grade inflammation and hypercoagulability

- Decreased thyroid function is associated with development of obesity and associated increased waist circumference that could potentially contribute to development of metabolic syndrome.

- Lower thyroid function can increase peripheral vascular resistence and activate the sympatho-adrenal system leading to increase in BP, particularly DBP

- Dysglycemia is more frequent among hypothyroid patients

- Metabolic syndrome constitutes a cluster of risk factors characterized by hypertension, atherogenic dyslipidemia, hyperglycemia, prothrombotic and proinflammatory conditions.

- Metabolic syndrome and its components are associated with higher risk of cardiovascular diseases.

- Metabolic syndrome and hypothyroidism are well established forerunners of atherogenic cardiovascular disease. Considerable overlap occurs in the pathogenic mechanisms of atherosclerotic cardiovascular disease by metabolic syndrome and hypothyroidism.

- Hence I undertook this study to compare the prevalence of metabolic syndrome among hypothyroid and euthyroid subjects and to aid in early screening of metabolic syndrome to prevent future complication

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

To study the prevalence of metabolic syndrome in newly diagnosed hypothyroid patients.

SECONDARY OBJECTIVE:

To compare the prevalence of metabolic syndrome in newly diagnosed cases of hypothyroidism and euthyroidism, to aid in early screening and prevention of complications.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

HISTORICAL REVIEW:

The history of Metabolic syndrome rewinds around 250 years ago, before the term metabolic syndrome was coined up. It was the Italian anatomist and physician Morgagni who found the association between obesity, hypertension, atherosclerosis, uric acid disorders and sleep apnea.

Nicole pauleseu stated that obesity with diabetes as consequent phases representing same pathology. Later Maranon in 1927 described AHT and obesity as pre-diabetic state. Thus in 1960's simultaneous presence of DM, AHT, increased lipid levels and obesity was mentioned as pleurimetabolic syndrome.

In 1980's Reaven, an endorcrinologist identified the association of insulin resistance and compensatory hyper-insulinism with pathological process of each components and called it as X syndrome. Dr. Ferranini confirmed the association and named it as Insulin Resistence Syndrome. X plus syndrome in addition to X syndrome associated aging and hyperuricemia. Anthony ceami the biologist identified that the long standing elevated blood glucose as a main factor in the accumulation of

advanced glycosylation end products which ultimately led to accelerated aging by its interaction with protein and collagen at cellular level.

The first definition of Metabolic syndrome was set by WHO in 1998 later EGIR (European Group for the study of Insulin Resistance) brought alteration in WHO definition proposing insulin resistance as main cause. In 2001 NCEP- ATP III criteria came into existence for defining criteria for MS, which do not include insulin resistance.

WHO criteria Table:

Insulin resistance, identified by 1 of the following:
• Type 2 diabetes
• Impaired fasting glucose
• Impaired glucose tolerance
• or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions
Plus any 2 of the following:
• Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
• Plasma triglycerides ≥150 mg/dL (≥1.7 mmol/L)
• HDL cholestero <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
• BMI >30 kg/m^2 and/or waist:hip ratio >0.9 in men, >0.85 in women
• Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g
Derived from Alberti et al[57,58]

HYPOTHYROIDISM

INCIDENCE OF HYPOTHYROIDISM:

The incidence of hypothyroidism varies according to the population studied [1,2]. Overt hypothyroidism is seen in about 0.3% of the population with elevated TSH levels and reduced freeT4 levels. Subclinical hypothyroidism is seen in about 4.3% of the population with elevated TSH levels with a normal freeT4 concentration. Subclinical hypothyroidism may progress to overt hypothyroidism. Incidence is more among women, elderly and some racial and ethnic groups[2]. The incidence of Neonatal hypothyroidism is 1 in 3500 cases[3]

INTRODUCTION

The name Thyroid is a greek word in which thyreos means shield and eidos means form. Thyroid gland consists of two lobes connected in between by isthmus. It is situated in between the cricoid cartilage and the suprasternal notch just anterior to the trachea. In its normal state, the gland weighs about 12 to 20 grams in size. Thyroid gland develops during third week of gestation from the floor of primitive pharynx and migrates along thyroglossal duct to the neck.

Thyroxine (tetraiodothyronine or T4) and Triiodothyronine (T3) are the hormones principally secreted from the thyroid gland. They are

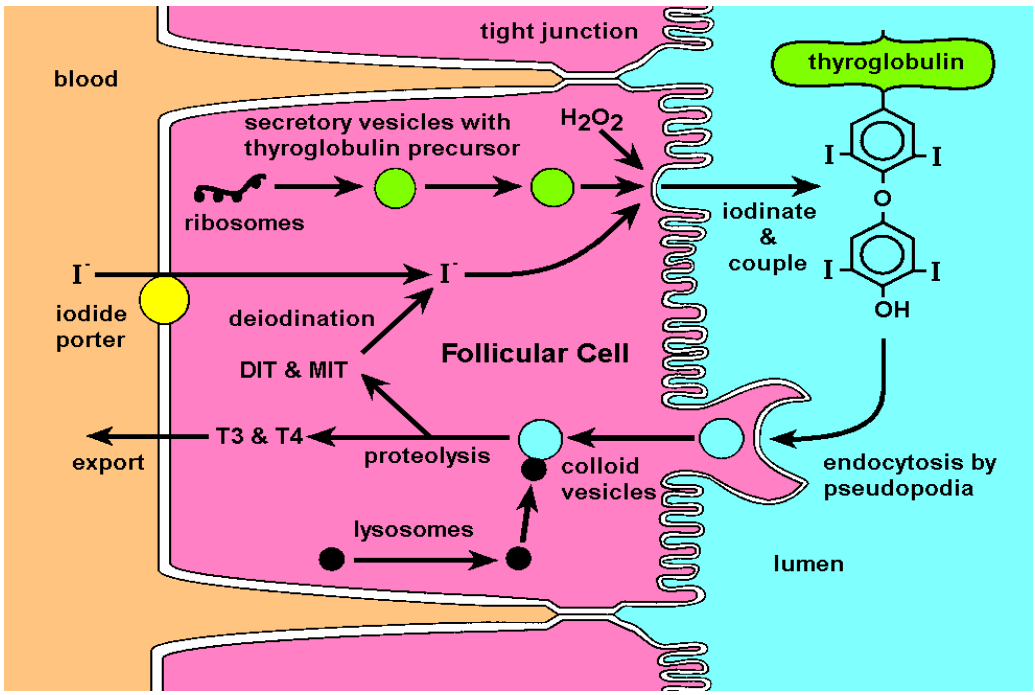
tyrosine based hormones responsible for the regulation of metabolism which is indeed more sensitive to minute changes in circulatory hormone level. Iodine is necessary for the production of thyroid hormones.T4 is the major form in blood and has a long half life than T3. T4 on deiodination can be converted to T3(by deiodinase) which is three to four times more active than T4. Ratio in blood is T4:T3 is 20 : 1 approximately. Further processing by decarboxylation and deiodination produces iodothyronamine and thyronamine. Selenium is essential for T3 production.

SYNTHESIS OF THYROID HORMONE

1. Transport of iodide into follicular cells is against electrochemical gradient which is linked with Na-I transport. This requires energy from oxidation. The transporeter is located in the basolateral membrane of the follicular cells [4]

2. Iodide then moves to apical side which is transported by iodide-chloride transporter pendrin to the exocytotic vesicles where iodide is oxidise and then bound to tyrosyl residues. This reaction involves hydrogen peroxide.

3. Two diiodotyrosine couples to form T4 and didiodo and monoiodotyrosine couples to form t3 which is also catalysed by peroxidise



4. Thyroglobulin is present in the lumen of follicles [5] it is synthesised in the RER and then transferred to exocytotic vesicles in the apical cell membrane. The formation of thyroid hormones occurs in the region of specific amino acid sequence[6]

5. The colloid which contains thyroglobulin is fused with tyrosine where it is hydrolyed and secreted into circulation. Recycling of iodide happens which is under control of gene that encodes iodotyrosidecleidonase [7].

PHYSIOLOGICAL EFFECTS OF THYROID HORMONES

Thyroid hormone targets each and every cell of the body and has profound effects on development, growth and metabolism.

DEVELOPMENT :

The development of the fetal and neonatal brain requires normal levels of thyroid hormones. This was demonstrated by a classical experiment in which the tadpoles failed to develop into frogs when they were deprived of thyroid hormone

GROWTH :

There is an intimately interwined growth promoting effect between thyroid hormone and growth hormone, which is evidenced by growth retardation in thyroid disorders.

METABOLISM:

Thyroid hormone is involved in diverse metabolic activities leading to increased metabolic rate.

Lipid metabolism → increased concentration of fatty acids in plasma due to fat mobilisation is seen in increased thyroid hormone levels. Oxidation of fatty acids is also enhanced. There is an inverse correlation between cholesterol and triglyceride levels and thyroid

hormone levels. Hypothyroidism is associated with increased blood cholesterol concentration.

Carbohydrate metabolism →Almost all aspects of carbohydrate metabolism are stimulated by thyroid hormones like Insulin dependent entry of glucose into the cells, gluconeogenesis , glycogenolysis to generate free glucose.

PHYSIOLOGICAL EFFECTS OF THYROID HORMONE

Cardiovascular system	Increases heart rate and cardiac output
Bone	Increases bone turnover and resorption
Respiratory system	Maintains normal hypoxic and hypercapnic drive in respiratory centre
Gastrointestinal system	Increases gut motility
Blood	Increases red blood cell 2,3-BPG[a] facilitating oxygen release to tissues
Neuromuscular function	Increases speed of muscle contraction and relaxation and muscle protein turnover
Carbohydrate metabolism	Increases hepatic gluconeogenesis/ glycolysis and intestinal glucose absorption
Lipid metabolism	Increases lipolysis and cholesterol synthesis and degradation
Sympathetic nervous system	Increases catecholamine sensitivity and β-adrenergic receptor numbers in heart, skeletal muscle, adipose cells and lymphocytes Decreases cardiac α-adrenergic receptors

[a]2,3-BPG, 2,3-bisphosphoglyceric acid.

OTHER EFFECTS:

CVS→ Thyroid hormones increase heart rate, force of contraction and cardiac output. Promote vasodilation and enhances blood supply to many organs.

CNS→ Decreased levels of thyroid hormones causes mental sluggishness and increased levels cause anxiety and nervousness.

REPRODUCTIVE SYSTEM→ normal levels of thyroid hormones are essential for normal reproductive behaviour and physiology. Hypothyroidism is most commonly associated with infertility.

CAUSES OF HYPOTHYROIDISM:

Hypothyroidism is the clinical state featured by reduced production of thyroid hormone. The permanent loss thyroid gland, by destruction due to radiation or autoimmune processes is called as primary hypothyroidism, which is the cause of 99% of hypothyroidism cases, and if such an impairment is progressive or transient then it will be typically associated with compensatory thyroid gland enlargement. Insufficient stimulation of the gland due to defect on hypothalamo or pituitary axis in producing thyroid stimulating hormone will result in central or secondary hypothyroidism

The cause may be from hypothalamus, pituitary or from the gland itself. Primary hypothyroidism is due to defect in the thyroid gland which is the most common, amongst which autoimmune i.e ., Hashimoto thyroiditis [8] is more common, especially in elderly female. Auto antibodies mainly against peroxidise and iodide transporters is frequent[9,10] . High level of iodine intake is associated with subsequent increase in auto antibodies[11]

CAUSES OF HYPOTHYROIDISM:

Primary
Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis
Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer
Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicylic acid, interferon- and other cytokines, aminoglutethimide, sunitinib
Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation
Iodine deficiency
Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis
Overexpression of type 3 deoiodinase in infantile hemangioma
Transient
Silent thyroiditis, including postpartum thyroiditis
Subacute thyroiditis
Withdrawal of thyroxine treatment in individuals with an intact thyroid
After ^{131}I treatment or subtotal thyroidectomy for Graves' disease
Secondary
Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies
Isolated TSH deficiency or inactivity
Bexarotene treatment
Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Smoking is also associated with autoimmune thyroiditis[12] Iatrogenic causes like thyroid surgery, radio-iodine , radiation may lead to hypothyroidism. Iodine deficiency, medications and substances competing with iodine like lithium, thiocyanide, tyrosinekinase inhibitors, antithyroid drugs and also ethionamide [13] cause hypothyroidism. Postpartum thyroiditis may lead to transient hypothyroidism.

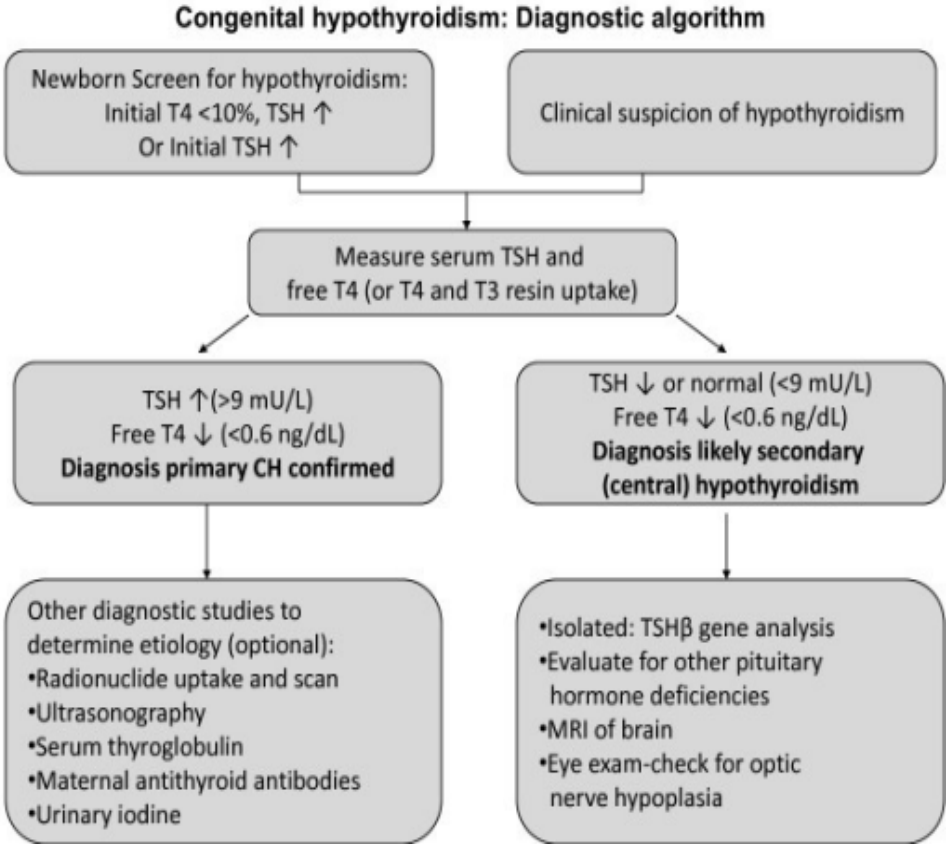
Secondary and tertiary causes are due to tumour of pituitary mainly micro-adenoma, and also sheehans syndrome, CNS trauma, infiltrative diseases and rarely resistence to T3 due to mutation of gene involving beta form of the nuclear receptor. Consumptive hypothyroidism due to increased breakdown of T3 T4 by T3 de-iodinase which is produced in ectopic site is also rare cause of hypothyroidism.

CONGENITAL HYPOTHYROIDISM:

Congenital hypothyroidism is one of the most preventable cause of mental retardation where exist inverse relation between age of diagnosis and beginning of treatment [14]. Earlier screening was done by heel stick blood [15]. It has male to female ratio of 2: 1 mainly due to ectopic thyroid than thyroid agenesis[16].

Most common cause is sporadic 85% and rest is hereditary due to inborn errors of synthesis. Central hypothyroidism in infants also had

other pituitary hormone insufficiency mainly to be doubted in infants with low blood sugar and micropenis. Inadequate treatment of maternal graves disease is also a cause if it is before 32 weeks of intrauterine life[17].



Transient hypothyroididsm in infants is due toiodine deficiency in mother and also due to blocking antibodies[18,19] maternal antithyroid treatment and other drugs like amiodarone [20] , radiographic contrast [21,22]. Large hemangiomas of liver producing type 3 deiodinase mutation in DUOX1 &DUOX2 gene are also rare causes.

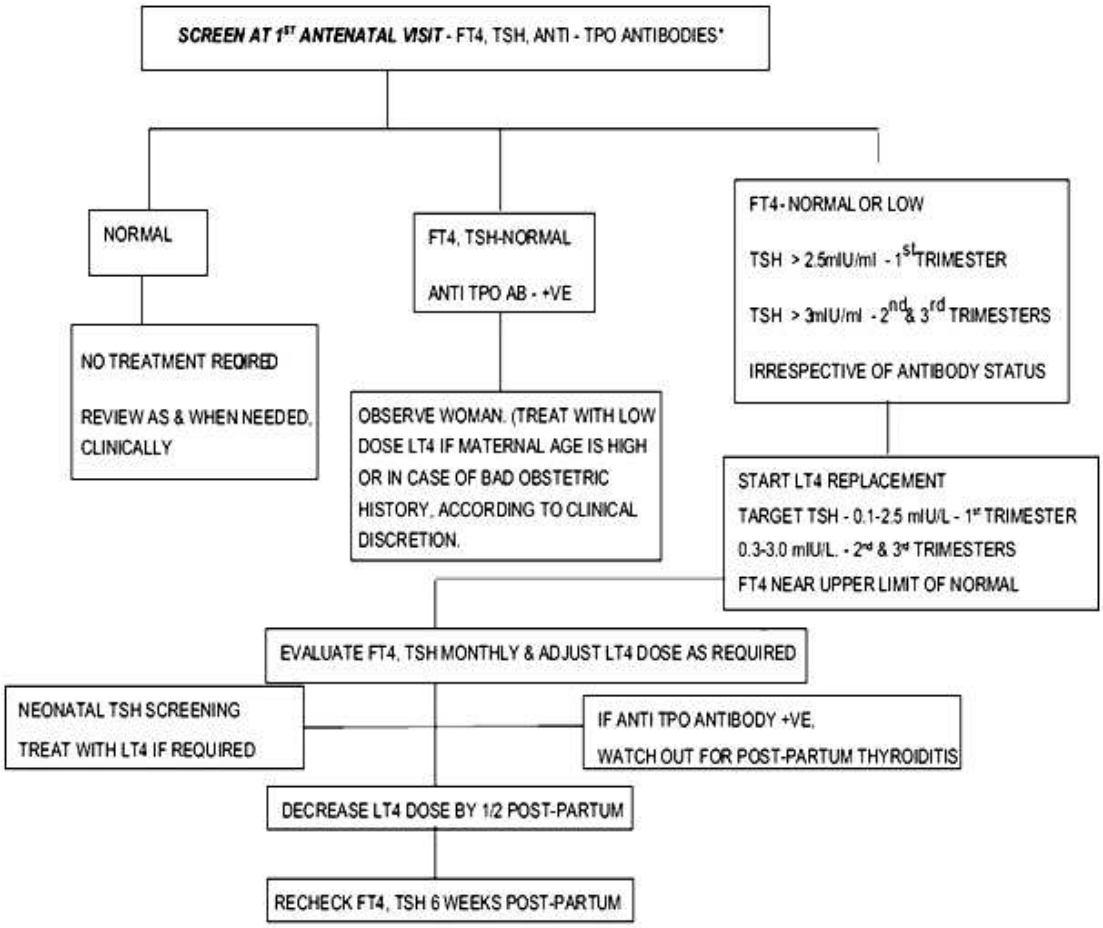
The clinical features manifested are increased birth weight than birth length, increased head circumference, decreased calcification of knee hypophysis, lethargy, feeding difficulties and macroglossia etc. associated malformation of heart, kidney, GIT, skeletal system is also prevalent in congenital hypothyroidism [23-27]. Infants with positive screening are further tested for TSH, free T3, T4 so confirm hypothyroidism which is followed by radionucleotide imaging, USG, urine iodine and autoantibodies to rule out the cause.

HYPOTHYROIDISM IN PREGNANCY:

The most common cause of hypothyroidism in pregnancy is Autoimmune thyroiditis. Hypothyroidism in subclinical state is usually assymptomatic. There is miscarriage risk [28] attributed to autoimmune thyroiditis. Even euthyroid antenatal women autoantibodies are at risk of miscarriage. So they are also treated with thyroxine[30] i.e like subclinical hypothyroid dose. Overt hypothyroidism is also associated with risk of diabetes.

Substance	Transfer across placenta
Iodine	Transferred avidly across placenta, both by passive diffusion and by active transport
Thyroxine	Some transfer is seen, especially in the first trimester
TSH	Poorly transferred
TRH	Avidly transported across placenta
Antibodies	Anti Tpo, Anti TG, TSI, TBII can all cause placenta freely and TSI can cause transient neonatal hyperthyroidism and TBII can cause transient neonatal hypothyroidism.

The presence of thyroglobulin in the amniotic fluid suggests the transfer of the hormone from mother to fetus which inturn is essential for development of the central nervous system of the fetus. It also protects the fetus from respiratory distress. There is increased risk of maternal diabetes, hypertension, abortion and postpartum hemorrhage in maternal hypothyroidism.



*MANDATORY FOR HIGH RISK WOMEN, PREFERABLE FOR ALL WOMEN

CLINICAL FEATURES OF HYPOTHYROIDISM:

SIGNS AND SYMPTOMS OF HYPOTHYROIDISM (DESCENDING ORDER OF FREQUENCY)	
Symptoms	**Signs**
Tiredness, weakness	Dry coarse skin; cool peripheral extremities
Dry skin	Puffy face, hands, and feet (myxedema)
Feeling cold	Diffuse alopecia
Hair loss	Bradycardia
Difficulty concentrating and poor memory	Peripheral edema
Constipation	Delayed tendon reflex relaxation
Weight gain with poor appetite	Carpal tunnel syndrome
Dyspnea	Serous cavity effusions
Hoarse voice	
Menorrhagia (later oligomenorrhea or amenorrhea)	
Paresthesia	
Impaired hearing	

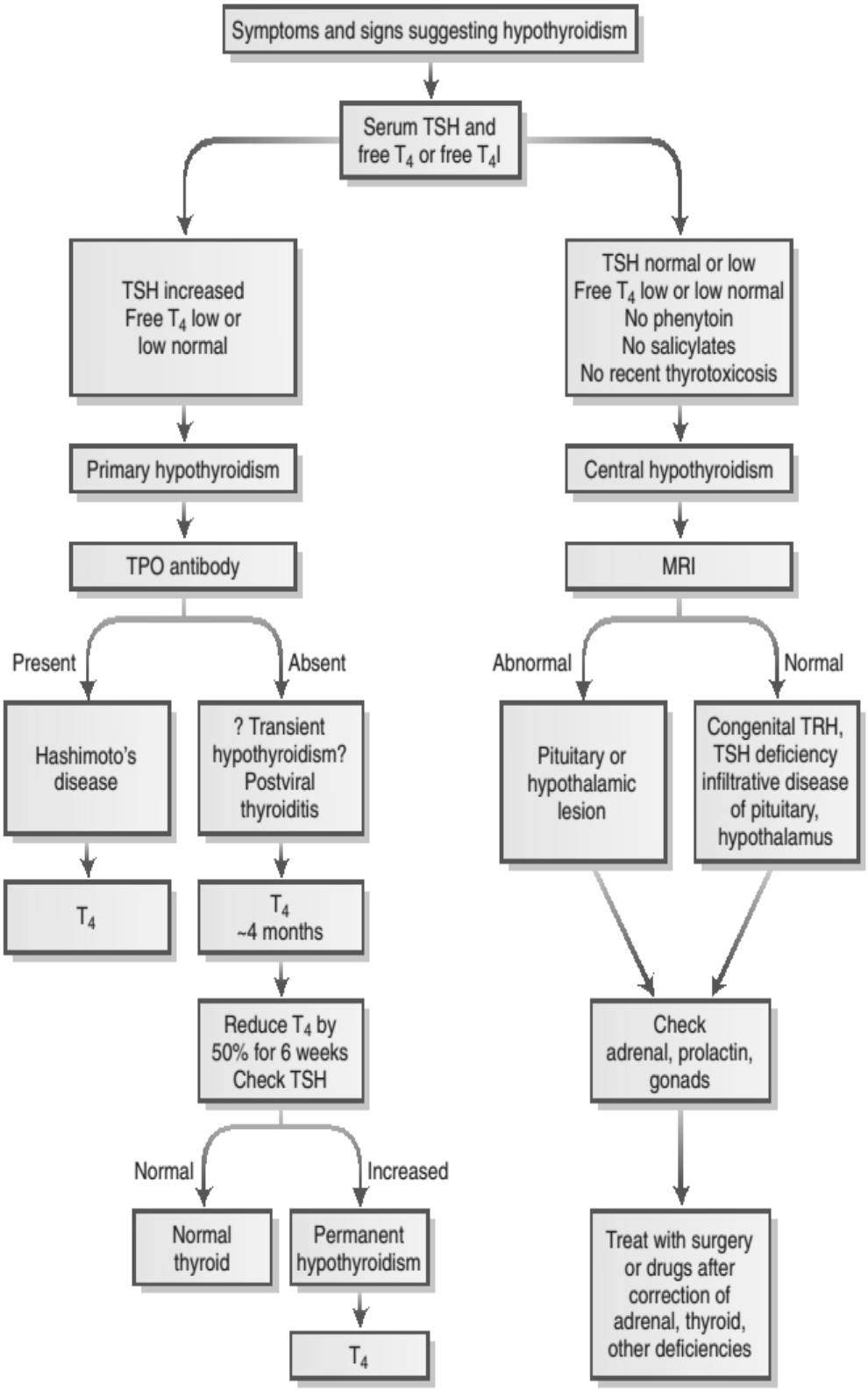
Clinical signs of hypothyroidism occurs due to absence of transcription of genes encoding calcium ATPase (Brent 1994) leading to prolonged relaxation and it also mobilises monopolysaccharides which is abnormally deposited in hypothyroidism. It also alters responsiveness of reticular activating system to catecholamines, alters the fluid and electrolytes homeostasis and also changes in blood flow.(beauretal 2008) The clinical manifestations are as shown in the table. Patients with very severe disease have very cold doughy skin, macroglossia, periorbital

puffiness, cardiomegaly and paralytic ileus. Most serious (jorden 1995) and rare complication of severe hypothyroidism is myxedema especially in elderly women with. It presents with decreased level of consciousness, decreased heart rate, decreased respiratory rate. Seizures may even occur due to altered metabolic parameters like hypoglycaemia and hyponatremia.

Another rare presentation is Hashimotos encephalopathy which can present as tremor opsoclonus myoclonus convulsion (chonj et al 2003, Castillo et al 2006). The people with hypothyroidism may also present with headache, bradykinesia, ataxia, even hearing loss, muscle weakness and sleep disorders like obstructive sleep apnea in patients with subclinical hypothyroidism

DIAGNOSIS OF HYPOTHYROIDISM:

Both clinical and lab inveastigations play a key role in diagnosis of hypothyroidism. Level of Thyroid stimulating hormone in subclinnial hypothyroidism is the key marker of dysfunction in euthyroid patients. T4, Antithyroid microsomal antibody testing as their presence indicating damage to thyroid gland causing hypothyroidism known as hashimotos thyroididtis. But these patients may initially present as hyperthyroidism due to release of stored thyroid hormones


Symptoms and signs suggesting hypothyroidism
Serum TSH and free T_4 or free T_4I
TSH increased Free T_4 low or low normal
TSH normal or low Free T_4 low or low normal No phenytoin No salicylates No recent thyrotoxicosis
Primary hypothyroidism
Central hypothyroidism
TPO antibody
MRI
Present
Absent
Abnormal
Normal
Hashimoto's disease
? Transient hypothyroidism? Postviral thyroiditis
Pituitary or hypothalamic lesion
Congenital TRH, TSH deficiency infiltrative disease of pituitary, hypothalamus
T_4
T_4 ~4 months
Reduce T_4 by 50% for 6 weeks Check TSH
Check adrenal, prolactin, gonads
Normal
Increased
Normal thyroid
Permanent hypothyroidism
T_4
Treat with surgery or drugs after correction of adrenal, thyroid, other deficiencies

METABOLIC SYNDROME

INTRODUCTION :

Metabolic syndrome is combination of metabolic abnormalities described in 1920 by kylin, in which he included hypertension, gout and diabetes. Then Vague observed upper body obesity associated with hyperglycemia and heart disease. Banting and Rever then named it as Syndrome- X though obesity is not included in it. Now metabolic syndrome is the most widely used terminology.

DEFINITION:

Recently WHO, Adult Treatment Panel III, NCEP ATP III and EGIR has framed definition for Metabolic syndrome all of which included BP, Abnormal lipid profile, Insulin resistance, and Obesity but the criterias are different. WHO insists on insulin resistance as major factor in metabolic syndrome. So elevated blood sugar in the form of impaired glucose tolerance is important for metabolic syndrome to be diagnosed. Along with this two more factors are needed.

EGIR definition has its utility more in epidemiological studies as it does not need euglycemic clamp for testing insulin sensitivity. So it is feasible in larger studies. It used Fasting blood sugar and also there is

change in cutoff range in hypertension, high density lipopretein level, waist circumference range and triglyceride levels

COMPARISION TABLE OF METABOLIC SYNDROME:

Clinical Measure	WHO (1998)	EGIR	ATP III (2001)	AACE (2003)	IDF (2005)
Insulin resistance	IGT, IFG, DM-2, or lowered insulin sensitivity* plus any 2 of the following	Plasma insulin _75th percentile plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of the following based on clinical judgment	None
Body weight	Men: waist-to-hip ratio ≥0.90; women: waist-to-hip ratio≥0.85 and/or BMI ≥30 kg/m2	WC≥94 cm in men or ≥80 cm in women	Waist circumference ≥102 cm in men or ≥88 cm in women	BMI ≥25 kg/m2	Increased WC (population specific) plus any 2 of the following
Lipid	TG >150 mg/dL and/ or HDL-C<35 mg/dL in men or <39 mg/Dl in women	TG ≥150 mg/dL and/ or HDL-C<35 mg/dL in men or <39mg/dl in women	TG≥150 mg/dL HDL-C _40 mg/dL in men or <50 in women	TG ≥150 mg/dL and HDL-C <40 mg/dL in men or<50 mg/	Triglycerides ≥150 mg/dL or on TG Rx HDL-C<40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or 85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	≥110 mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)
Other	Microalbuminuria			Other features of insulin resistance	

BMI, body mass index

ATP III:

It was actually proposed as a programme for presenting heart diseases which mostly involved obesity as a key factor. Now AACF has included fasting and post -prandial blood sugar level in the criteria for diagnosis of metabolic syndrome. Since there is an imminent need for simple definition as a tool for identification for risk in clinical practice.

NCEP ATP III Proposed Diagnostic Criteria of Metabolic Syndrome	
Diagnostic Criteria (any 3 below)	**Defining Points**
Elevated waist circumference[a]	Men: >102 cm (>40 in) Women: >88 cm (>35 in)
Elevated TG	≥150 mg/dL *OR* Drug treatment for elevated TG
Reduced HDL-C	Men: <40 mg/dL Women: <50 mg/dL *OR* Drug treatment for reduced HDL-C
Elevated blood pressure	≥130 mmHg systolic blood pressure *OR* ≥85 mmHg diastolic blood pressure *OR* Drug treatment for hypertension
Elevated fasting glucose	≥100 mg/dL *OR* Drug treatment for elevated glucose

Central obesity is calculated by waist circumference using guidelines set for gender and various ethnic groups. Here the cutoff points are based on the ethinicity not on the basis of where the people is actually residing. This is to be used in epidemiological studies which involve large study population and various ethnic groups.

ADDITIONAL METABOLIC PARAMETERS UNDER RESEARCH

There are other factors that appear to be associated in metabolic syndrome which are to be utilised in forthcoming research studies as they improvise the predictabily of risk involved in cardiac diseases and diabetes. These additional parameters thereby alter the definition leading to new set of criterias for better assessment of risk factors.

Definitions of MBS for women, according to WHo, NCEP ATP III and IDF Criteria

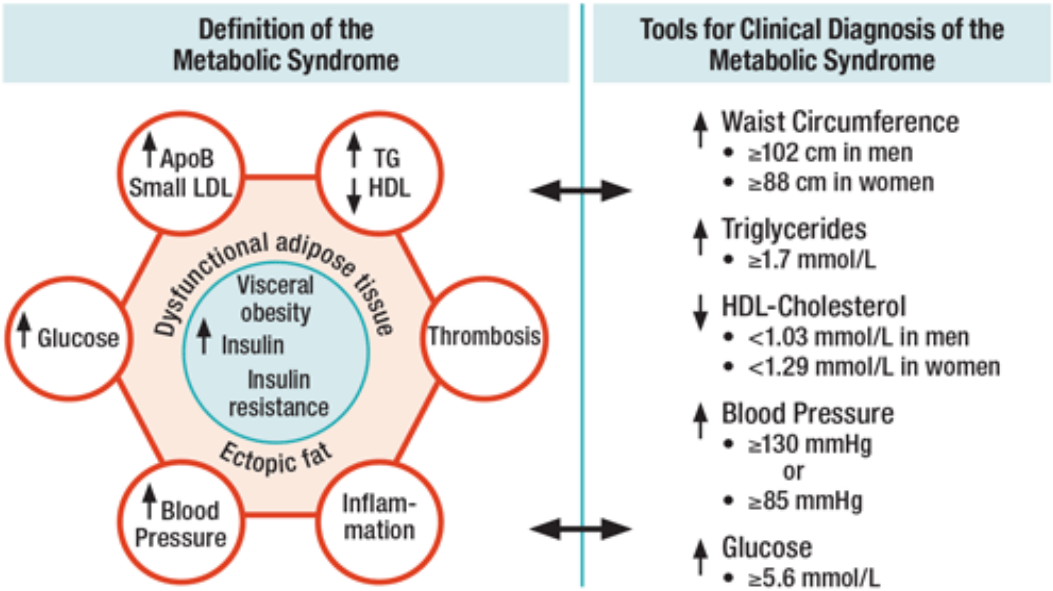
WHO	NCEP ATP III	IDF
T2D or IFG or IGT or insulin resistance plus ≥ 2 of the following: • BMI > 30 kg/m² or WHR > 0.85 • HDL < 1.0 mmol/L (< 40 mg/dL) • TG ≥ 1.7 mmol/L (150 mg/dL) • BP ≥ 140/90 mmHg or use of blood pressure medication • microalbuminuria > 20 pg/min • Alb/Crea ratio ≥ 30 mg/g	≥ 3 of the following: • WC ≥ 88 cm • HDL < 1.3 mmol/L (< 50 mg/dL) • TG ≥ 1.7 mmol/L (150 mg/dL) • BP ≥ 135/85 mmHg or use of blood pressure medication	Central obesity defined as WC above the ethnicity-specific cut-off plus ≥ 2 of the following: • TG ≥ 1.7 mmol/L (150 mg/dL) or specific treatment • HDL < 1.3 mmol/L (< 50 mg/dL) or specific treatment • BP ≥ 135/85 mmHg or use of blood pressure medication • fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL) or previously diagnosed T2D

INTRODUCTION

Metabolic syndrome comprise of components as follows:

- BP
- DM
- HYPERCHOLESTEROLEMIA
- OBESITY
- INSULIN RESISTENCE

The distribution of these parameters includes elevated cholesterol, elevated BMI, as most commonly involved metabolic parameters. These parameters are followed by other parameters like HBA1C, increased blood sugar, albuminuria, which are less common. Increased risk of cardiovascular disease is mainly influenced by elevation of blood glucose and occurrence of proteinuria which pose greatest threat for development of cardiovascular disease. Amongst all these risk factors higher lipid levels exist as the most common parameter in combination components.

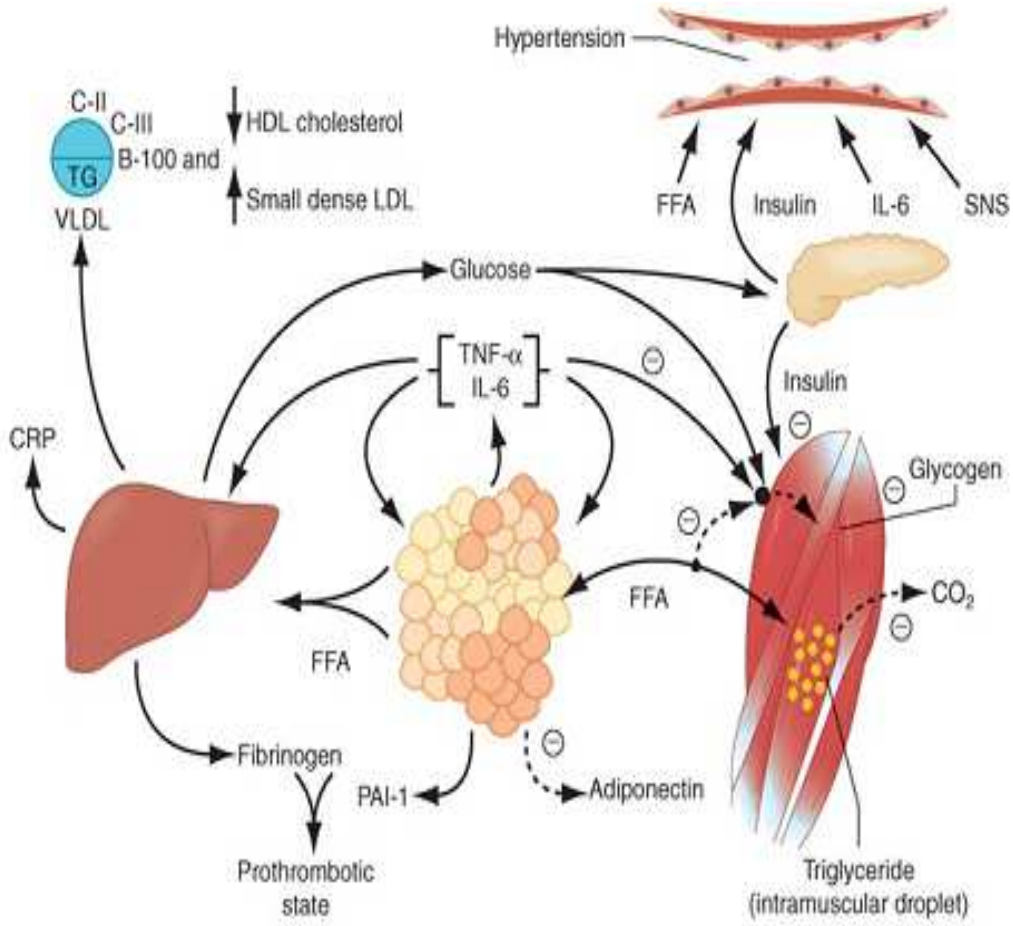


PATHOPHYSIOLOGY OF METABOLIC SYNDROME:

- Adipose tissue releases FFA which causes high glucose, TGs and VLDL, associated with high LDL and low HDL.

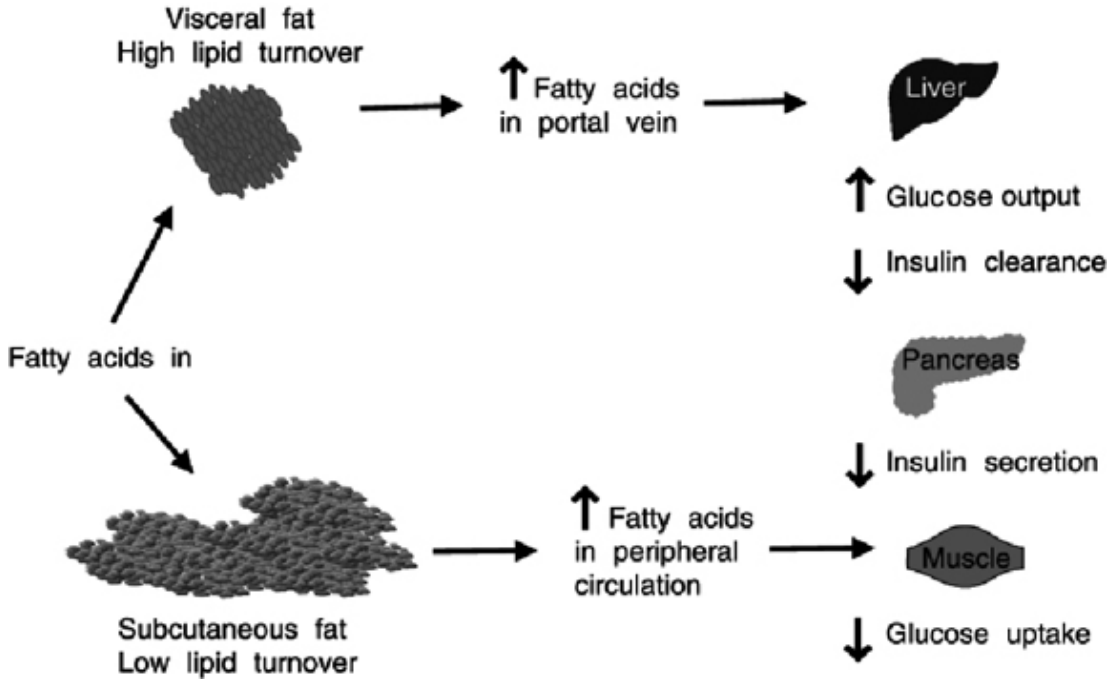
- FFA also decrease sensitivity of insulin in muscle, leading to inhibition of glucose uptake which is insulin mediated.

- Increased free glucose in circulation increases insulin release from pancreas causing hyperinsulinemia leading to high Na+ absorption and SNS activity causing hypertension



OBESITY:

Among different type of diabetes mellitus, the relationship of obesity is complex as we some diabetic patients with lean stature. Obesity is forerunner of diabetes due to insulin resistence [31,32] . The reason for obesity varies in different types amongst which genetic disposition is most clearly involved [49,50,51] so decreasing obesity is the main stay of treatment.



PATHOPHYSIOLOGY OF OBESITY :

FFA is the main source of energy to skeletal muscle kidney and liver. It is the main source of triglyceride production for liver. During starvation it provides alternate source to glucose. The free fatty acid leads to increased oxidative stress during its utility as energy source leading to metabolic syndrome[33,34]. As lipogenesis is inhibited clearance of triacylglycerol is decreased due to hyper-triglyceridemia. This leads to liberation of endothelial lipoprotein lipase which ultimately ends in insulin receptor dysfunction. Resistance to insulin increases the generation of glucose from live r and increase free fatty acid leads to decreased utility of glucose exaggerating the hyperglycemia even more[35,36]

Country/ethnic group	Waist circumference value	
	Male	Female
Europids*	≥94 cm	≥80 cm
South Asians‡	≥90 cm	≥80 cm
Chinese	≥90 cm	≥80 cm
Japanese	≥85 cm	≥90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

*In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes, ‡Based on Chinese, Malay and Asian-Indians populations

Adipocytes release adipokines namely lectin, vistatin, nectin, which along with insulin regulates fat mass in the body[37,38], not only proteo-homones but also inflammatory adipokines like cytokines, TNF alpha, interleukin 1,6 are released, so increased fat content as in obesity leads to increased co-morbid conditions like type 2 DM[39], insulin resistence, non alcoholic steato-hepatitis and injury to pancreatic beta cells decreasing the secretion of insulin. This is counter balanced by anti inflammatory adipokines like leptin and resistin which leads to atherogenic tendency.

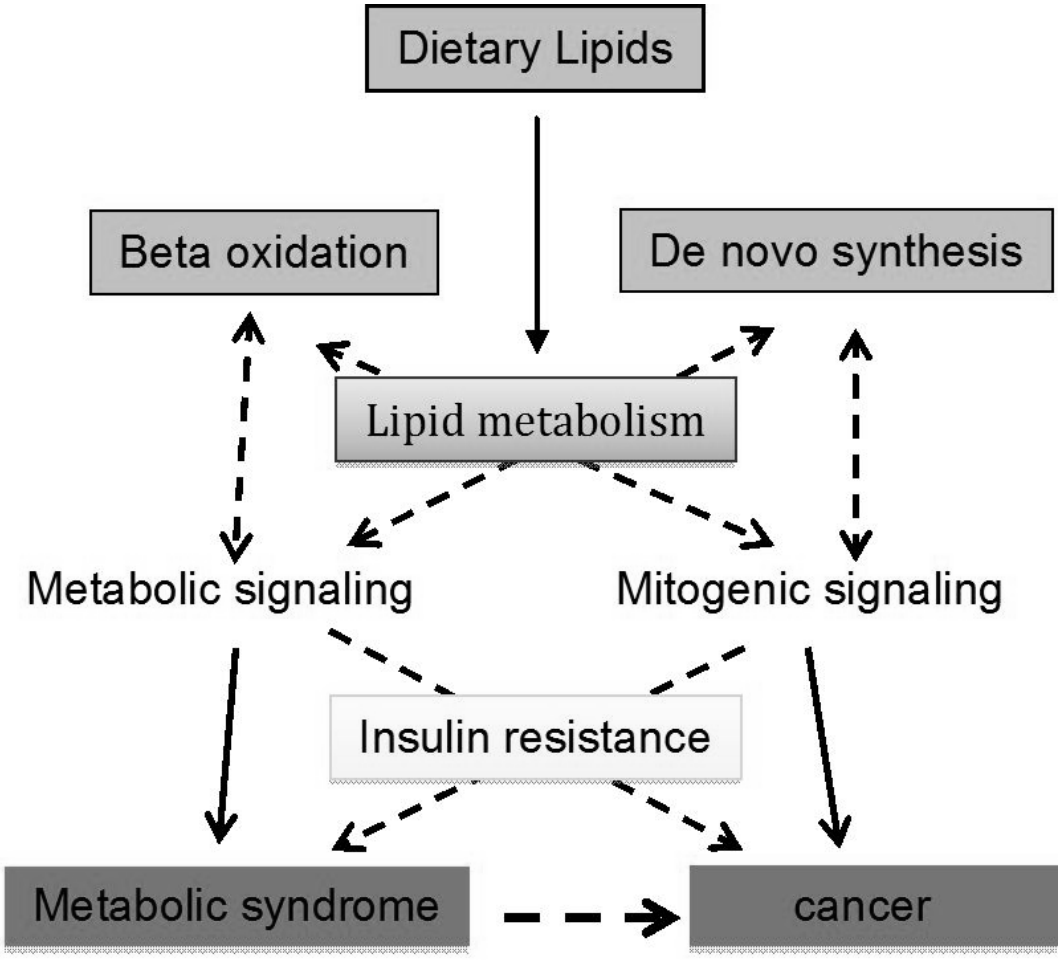
CLINICAL MANIFESTATIONS OF OBESITY:

Obesity leasds to co-morbidities like type2 DM, dyslipidemis, increased blood pressure, atherogenesis, non-alcoholic steato-hepatitis, obstructive sleep apnea. In all these cases inflammatory mediators leads to altered immune response. Obesity is also a risk factor for carcinoma colon as it involves apoptosis, inflammation, cellular proliferation along with gene expression and toxins. Men with high BMI had increased death rate in carcinoma prostate when compared with men having normal BMI[40]

Adults (>18 years of age)	Body mass index (kg/m²)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25–29.9
Obese	≥30
Class 1	30–34.9
Class 2	35–39.9
Class 3	≥40
Class 4	≥50
Class 5	≥60

CARCINOMA AND OBESITY:

Hepatocellular carcinoma is associated with obesity since fatty liver in obesity can progress to cirrhosis which inturn may be risk for carcinoma liver. Leptin is also a risk factor leading to increased growth of carcinomas[41] .



The inflammatory adipokines increases blood sugar and Hyperinsulinemia along with inflammatory mediators cause beta cell inflammation and dysfunction. Pancreatic dysplasia which occurs due to chronic inflammation in cases of chronic pancreatitis may promote the

development of adenocarcinoma of pancreas[42,49] .Adiponectin which is a adipokine secretogogue prevents angiogenesis. But in obesity there is decreased level of adiponectin when compared to proinflammatory adipokines promoting carcinoma[43,44]. Oestrogen is also associated with cancer of breast,prostate and ovary. Genes have key role in the cancer along with the above mentioned risk factors.

OBESITY AND GALL STONE:

In obesity, increased removal of cholesterol during fasting increases the secretion of cholesterol into bile leading to gall stone development[47]. These gall stones when chronically present can induce inflammation leading to risk of development of gall bladder cancer.

OBESITY AND JOINT DISEASE:

Joint disease are exaggerated in obesity due to the inflammatory mediators like resistin[45,46] and weight bearing.

RESPIRATORY SYSTEM AND OBESITY:

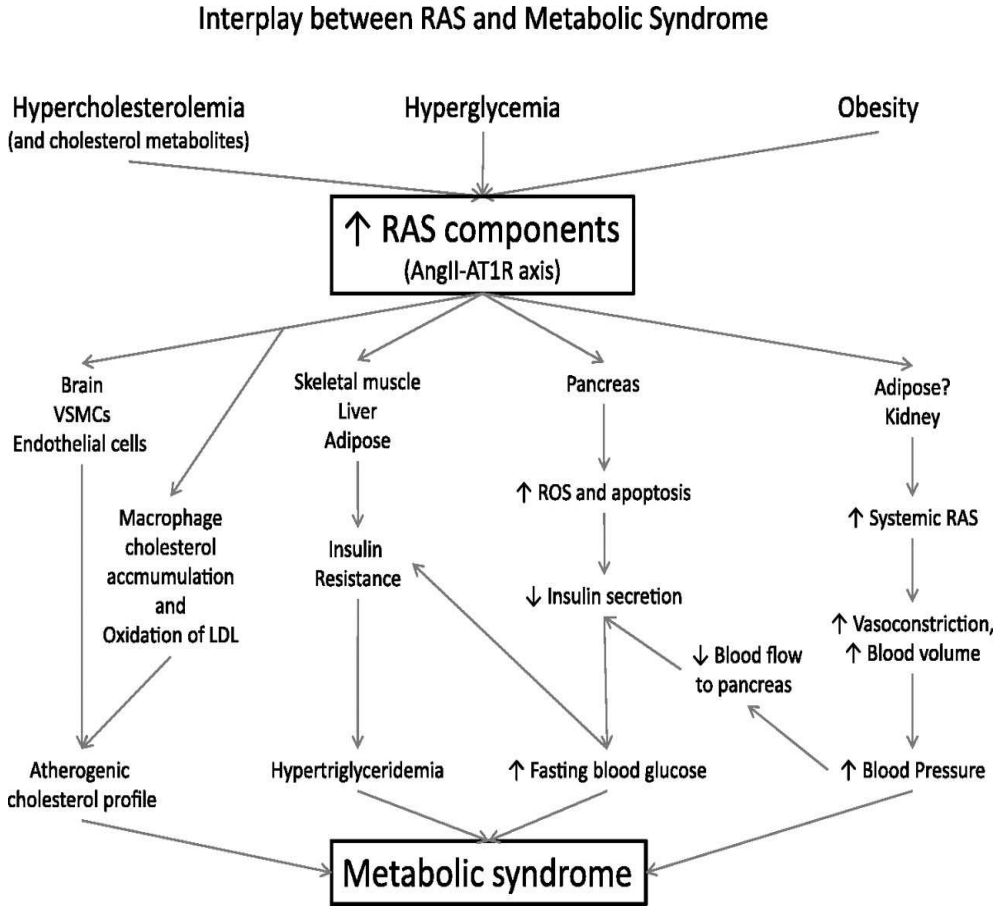
Obese persons are more prone for diseases of respiratory system. Obesity leads to increased deposition of fat in the upper respiratory tract leading to obstructive sleep apnea. It may also lead to hyoxia and even increased carbondioxide retension. In the region of bronchus these adipose tissue release inflammatory adipokines resulting

in asthma. Patients who were in prolonged state of deceased mobility are at higher risk of pulmonary embolism especially when they are obese[48]

OBESITY-RELATED ORGAN SYSTEMS REVIEW	
Cardiovascular	**Respiratory**
Hypertension	Dyspnea
Congestive heart failure	Obstructive sleep apnea
Cor pulmonale	Hypoventilation syndrome
Varicose veins	Pickwickian syndrome
Pulmonary embolism	Asthma
Coronary artery disease	**Gastrointestinal**
Endocrine	Gastroesophageal reflux disease
Metabolic syndrome	Nonalcoholic fatty liver disease
Type 2 diabetes	Cholelithiasis
Dyslipidemia	Hernias
Polycystic ovarian syndrome	Colon cancer
Musculoskeletal	**Genitourinary**
Hyperuricemia and gout	Urinary stress incontinence
Immobility	Obesity-related glomerulopathy
Osteoarthritis (knees and hips)	Hypogonadism (male)
Low back pain	Breast and uterine cancer
Carpal tunnel syndrome	Pregnancy complications
Psychological	**Neurologic**
Depression/low self-esteem	Stroke
Body image disturbance	Idiopathicintracranial hypertension
Social stigmatization	Meralgia paresthetica
Integument	Dementia
Striae distensae	
Stasis pigmentation of legs	
Lymphedema	
Cellulitis	
Intertrigo, carbuncles	
Acanthosis nigricans	
Acrochordon (skin tags)	
Hidradenitis suppurativa	

OBESITY AND PRE-ECLAMPSIA:

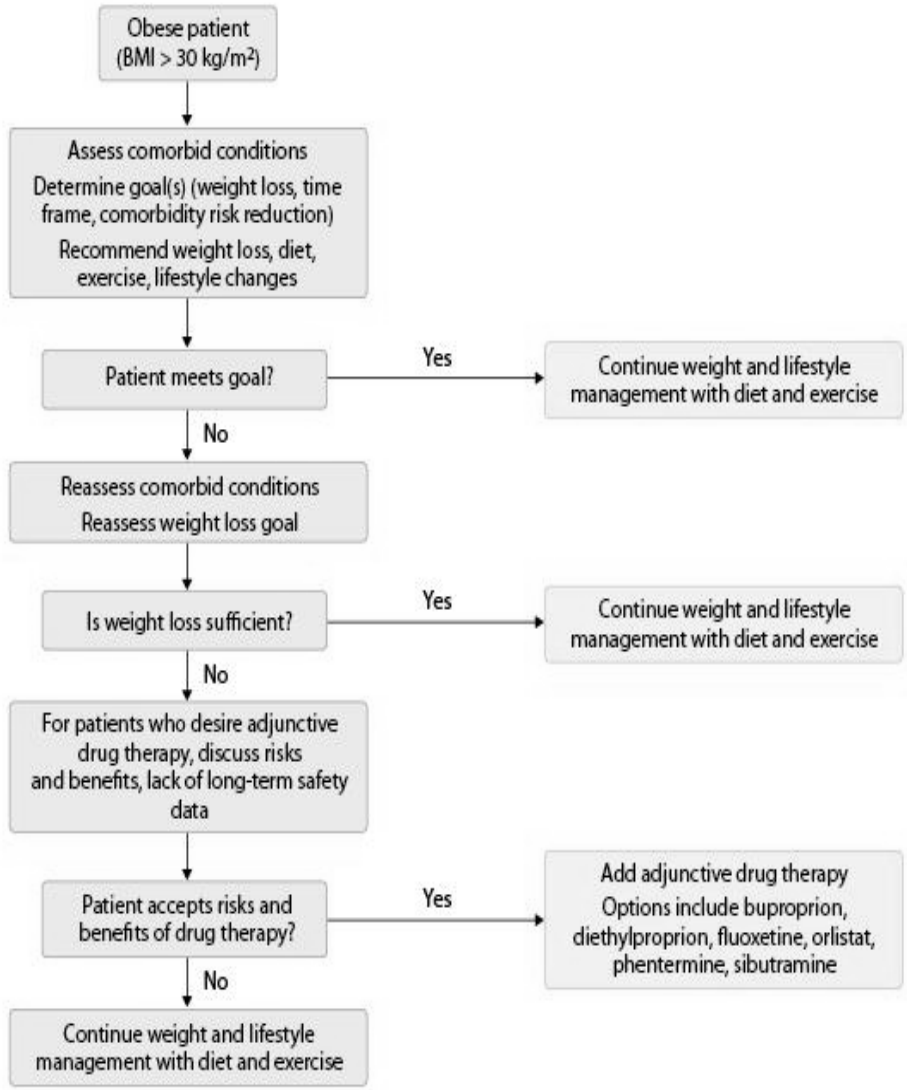
Obesity is also risk factor for pre-eclampsia as these inflammatory adipokines include derivatives of substance like prostaglandins, RAS which are involved in the development of pre-ecclampsia .



Obesity is a key factor in polycystic ovarian syndrome in which the secretogogues released from adipose tissue leads to metabolic derangements. Apart from pre-eclampsia, PCOS, hypertension and obesity may also cause depression, urinary stress incontinence, amenorrhea and poor wound healing. Most of the disorders can improve with reduction of BMI.

MANAGEMENT OF OBESITY:

A Guide to Selecting Treatment					
	BMI Category				
Treatment	**25–26.9**	**27–29.9**	**30–35**	**35–39.9**	**40**
Diet, exercise, behavior therapy	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy	With comorbidities		+	+	+
Surgery				With comorbidities	+



FUNCTIONS OF INSULIN:

Insulin Function		
Liver	Adipose Tissue	Muscle
↓ glycogenolysis	↓ lipolysis	↓ protein catabolism
↓ gluconeogenesis	↑ glycerol formation	↓ amino acid oxidation
↓ ketogenesis	↑ fatty acid formation	↑ amino acid uptake
↑ glycogen synthesis	↑ glucose uptake	↑ glucose uptake
↑ fatty acid synthesis		↑ protein synthesis
		↑ glycogen synthesis

INSULIN RESISTENCE

INTRODUCTION:

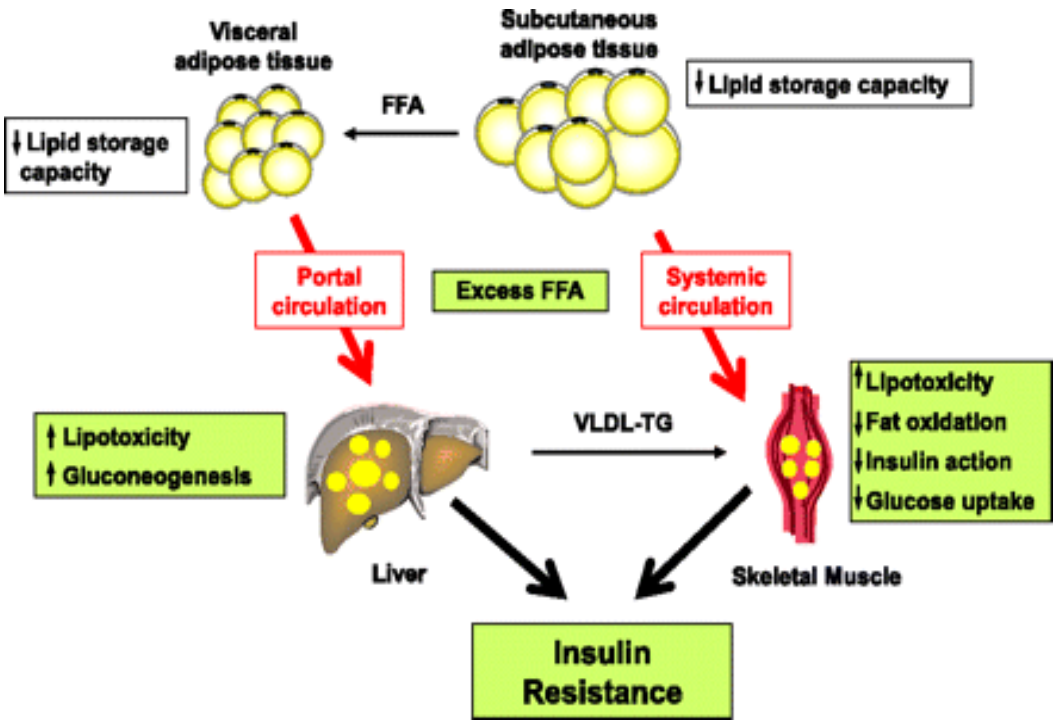
Earlier it was widely accepted that diabetes was mainly due to deficiency of insulin secretion. Later after ten years of discovery of the hormone in 1922 by Banting and Best, it was proposed that it is insulin resistance and not the deficiency which leads to type 2 diabetes. Berson together with Yalow demonstrated that people with type 2 diabetes had higher levels if insulin, which was later corroborated by Roth[52] and Reaven[53,54]

PATHOPHYSIOLOGY:

The pathogenesis of insulin resistance is defect in metabolism involving muscles fat liver and beta cell of pancreas. Insulin resistance has genetic predisposition which is further fuelled by obesity. When the beta cells are not able to compensate for insulin resistance then glucose tolerance occurs. Increased fatty acid generation by adipose tissue and increased glucose production by liver accompanied with failure of beta cell to produce insulin leads to exogenous insulin requirement.

Insulin resistance apart from type2 DM is the source of risk in other disease states like coagulation disorder, abnormal lipid profile,

weight gain hypertension, atherosclerosis, PCOD, together known a Syndrome-X[55]



MECHANISM OF INSULIN RESISTANCE

Primary abnormality leading to insulin resistance is the defect in transport of glucose into the skeletal muscle. Defect in insulin receptor phosphorylation and subsequent phosphotidyl inositol 3 kinase action by fatty acid leads to defective glucose transport across the skeletal muscle. Understanding the underlying defects leading to insulin insensitivity will pave way for identification of newer therapeutic targets.

The fact of insulin resistance leading to type II DM is supported by

(i) Offsprings of patients with typeII DM having insulin insensitivity

(ii) Prevention of hyperglycemia by agents which sensitize insulin.

Nowadays there is a shift from glucocentric view to lipocentric view of insulin resistance. Ectopic deposition of lipid contributes to insulin sensitivity which is known as lipotoxicity. Derangement in the metabolism of fatty acid leads to abnormal deposition of lipid causing insulin resistance. Though indices like BMI ,waist circumference, waist/ hip ratio, measurement of lipids inside the muscle cells by MR Spectroscopy is the one which associates insulin resistance more closely to obesity[56]

In lipodystrophy there is limited availability of lipid storage depot and decreased leptin leading to overeating. In lipotoxicity there is surplus lipid. Replacing adipose tissue in lipodystrophy leads to decrease in intake of energy and insulin sensitivity.

MUSCLE GLUCOSE METABOLISM IN INSULIN RESISTANCE:

13C MRS is a novel method to measure intramuscular glucose level. Through this study, it is observed that in normal people 80% of glucose uptake is converted to glycogen and stored in muscle as a source of glucose to be used when needed. The two organs which store glucose

in the form of glycogen is muscle and the liver. So in diabetes stored level of glycogen in these organ is reduced. So utility of this method is to detect the rate limiting aspect in diabetogenesis responsible for defect in storage of glucose as glycogen.

31P MRS and 13C MRS were used to measure concentration of glycogen and glucose 6P. This is done in the state of hyperglycemia and hyperinsulinemia phase. G6P is intermediate and its phosphorylation by the enzyme hexokinase which leads to subsequent glycogen formation. In this method it was observed that there is increase in concentration of glucose 6P.

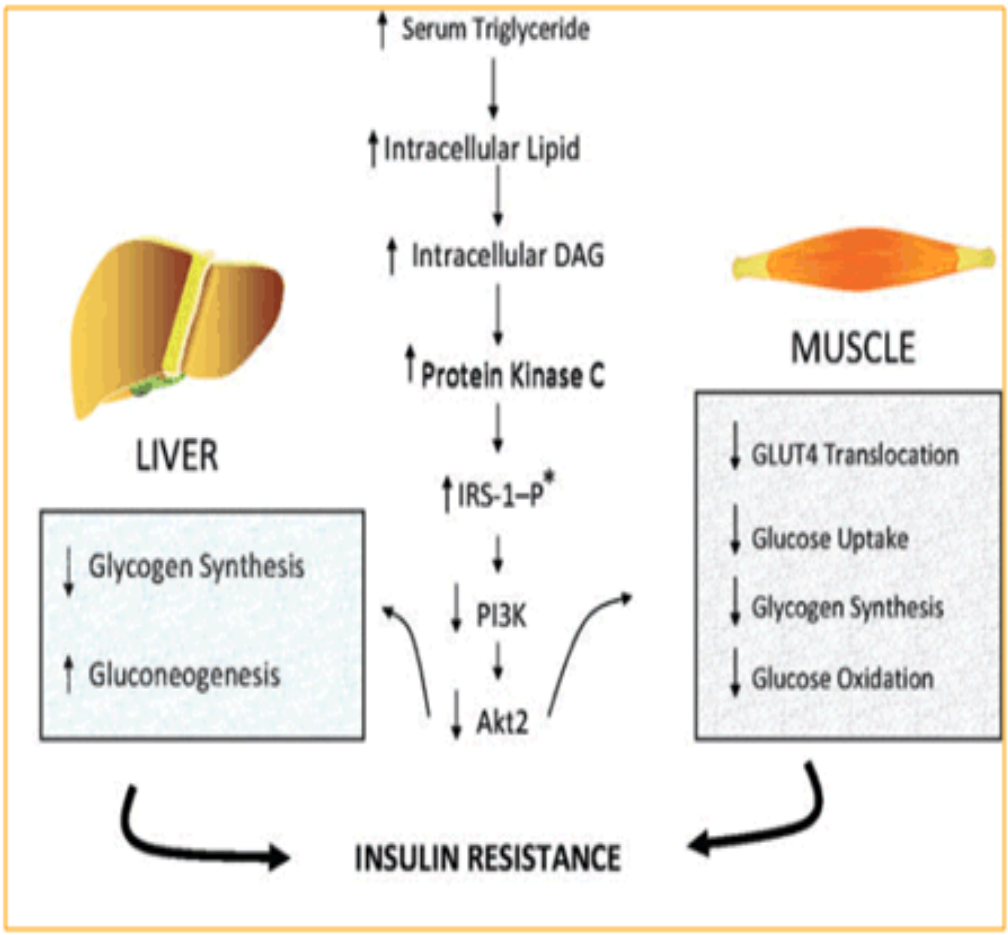
In diabetes the concentration of G6P inside is less, indicating that either glucose transport inside the muscle or its phosphorylation are the steps which control the rate. The same is observed in the offsprings of the patients with type2 DM who were resistant to insulin. Now in order to identify either glucose transport or its phosphorylation is defective. 13CMRS method is used to measure free glucose level inside the muscle. It was found that intracellular glucose level in skeletal muscle is low indicating it is the transport of glucose that is rate controlling for synthesis of muscle glycogen by stimulation of insulin in type 2 DM patients.

LIPID MEDIATED RESISTANCE TO INSULIN

It was found that infusion of lipids to elevate the concentration of fatty acids led to reduced disposal of insulin mediated glucose transport. But decrement in sensitivity of insulin happened only several hours after the increase in concentration of fatty acid . This delay in sensitivity of insulin is because of increase in oxidation of fatty acid would lead to increase in NADH : NAD ratio. This leads to inactivation of the enzyme pyruvate dehydrogenase, this inturn led to elevated levels of intracellular citrate. The citrate elevation inhibits the enzyme phosphofructokinase. This is followed by accumulation of G6P. As the G6P inhibits the activity of enzyme hexokinase there is increased accumulation of glucose inside the cell there by leading to decreased uptake of glucose by muscle cells.

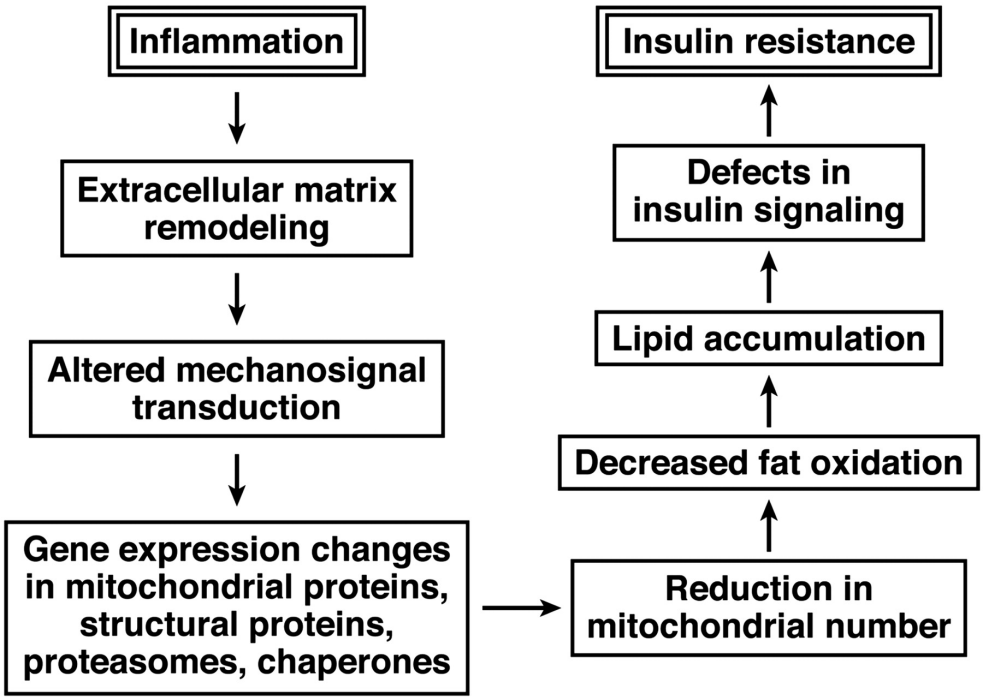
In type 2 DM there is decrease in level of intracellular G6P rather than elevated level as described by the hypothesis. This lead to the possibility of alteration in the activity of trafficking of insulin mediated GLUT4 in between the inside of cell and cell membrane. The fact observed was that insulin receptor substrste -1 (IRS-1) associated P13 kinase action was decreased to significant extent under the condition of lipid infusion . So it may be the increased fatty acylCOA or other

derivatives of fatty acid inside the liver and muslce can cause resistance of insulin based on more delivery or decreased metabolism of glucose.

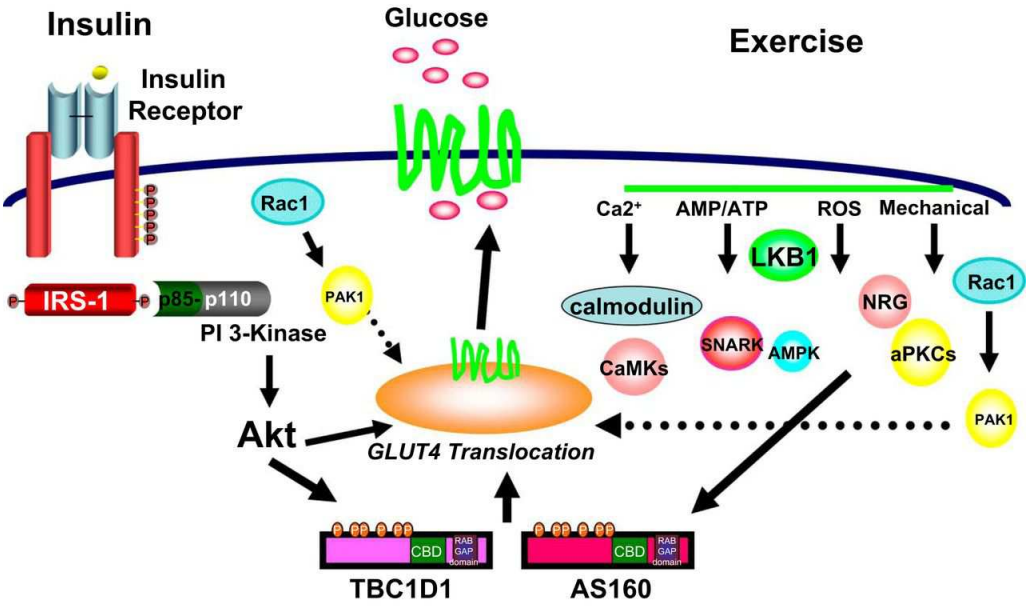


INFLAMMATION AND INSULIN RESISTANCE:

Apart from adipokines proinflammatory TNF alpha secreted by monocytes affects the coagulation profile and function of endothelium.



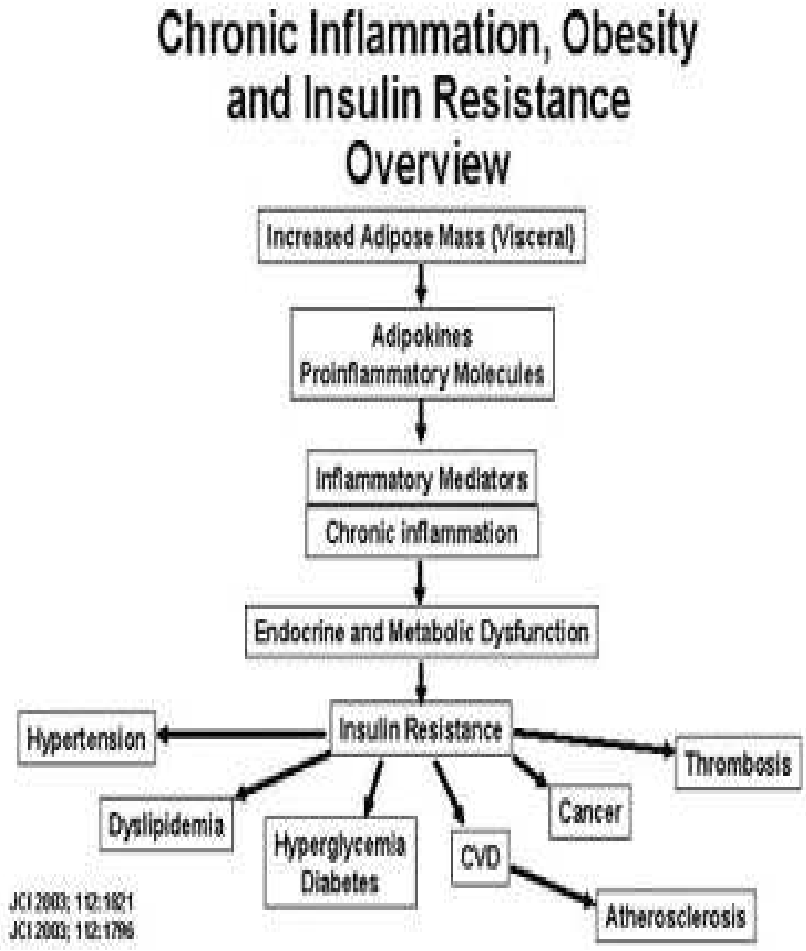
There is decreased expression of IRS and gene of GLUT4 leading to reduced uptake of insulin dependent glucose [(59)]. Genes like HSL ADIPOQ and nuclear receptors like RXR and the PPAR- g are responsible for the maintaining of glucose homeostasis. The altered expression of the above mentioned genes by change in the expression of adipocytes led to insulin insensitivity . Salicylates repress Ikkb leading to protection from resistence to insulin in obesity. LISR produced by liver presents lkkb activation protecting hepatic resistance to insulin. The activation of genes that codes iNOS lead to increased resistance to insulin [(60)].



Insulin resistance in patients with sepsis is mediated by iNOS s- nitrosylation of IRS and Akt [61,62]. IL-10, the anti inflammatory agent produced by leukocytes is used in treatment of resistance to insulin.

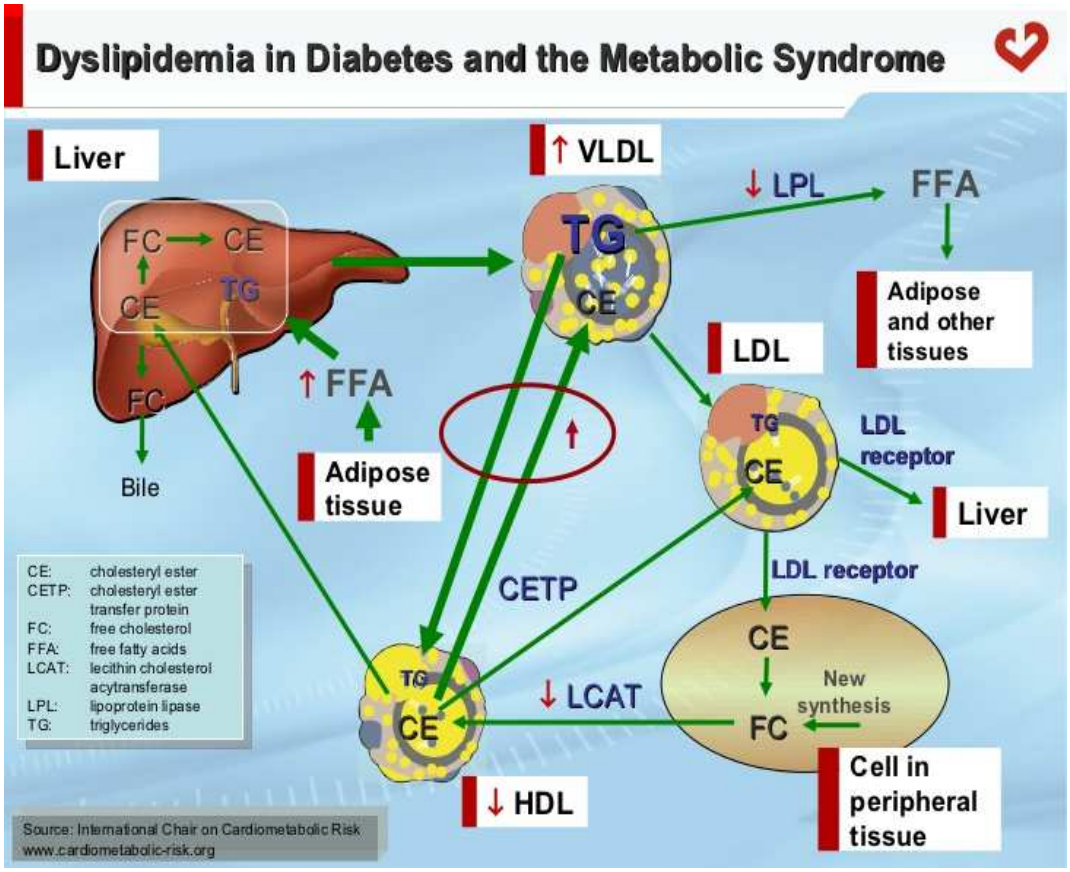
The down regulation of genes encoding macrophage expression also helps in increasing sensitivity to insulin.

Thiazolidinediones used in insulin resistance is based on this mechanism[63]. Cognate receptor, chemokine receptor -2 and monocyte chemoattractant protein-1(MCP) which induced the movement of monocytes to the tissues which were inflammed lead to increased insulin sensitivity.



DYSLIPIDEMIA IN METABOLIC SYNDROME:

In dyslipidemia increased formation of VLDL ApoB100 and their decreased catabolism and increased HDL degradation leads to metabolic syndrome.

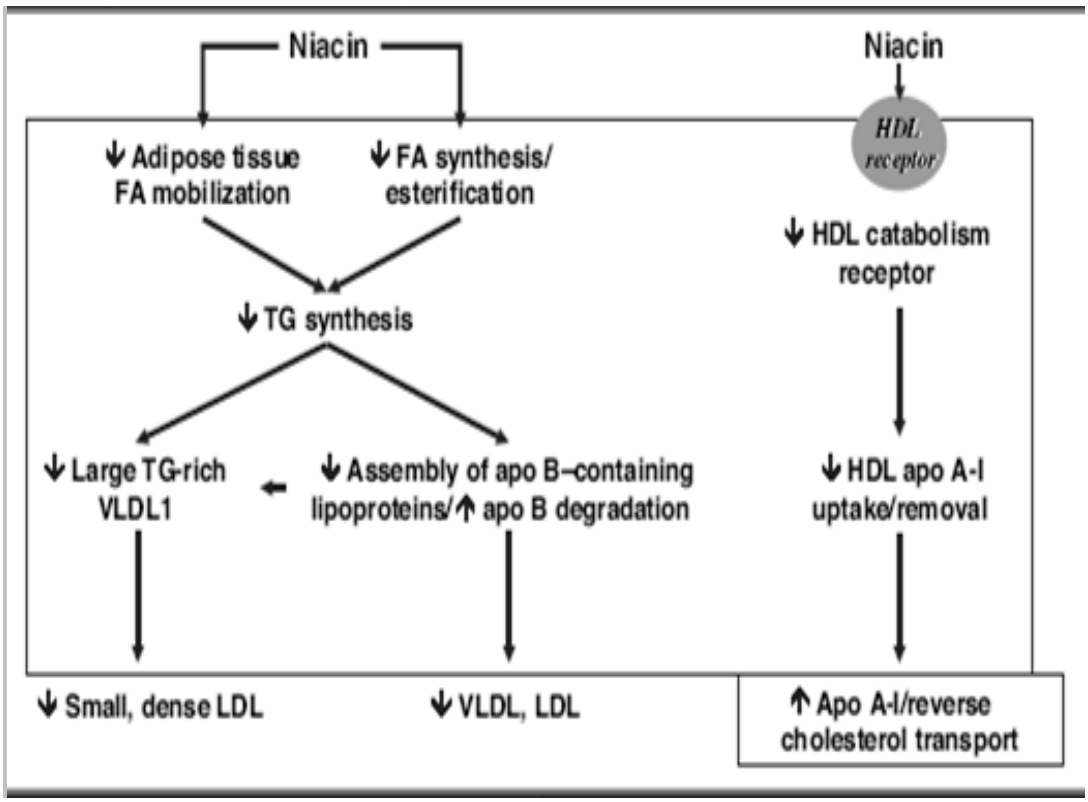


The insufficient esterification of free fatty acids and increased resistance to insulin both can lead to increased fatty acids to liver leading to increased VLDL ApoB and increased clearance of HDL. The liver obtains more FA from circulation which induces triglyceride synthesis which leads to increased VLDL and increased ApoB formation from liver . In case of insulin resistance more insulin is present, in such a circumstance the inhibitory effect of insulin on secretion of VLDL is reduced.

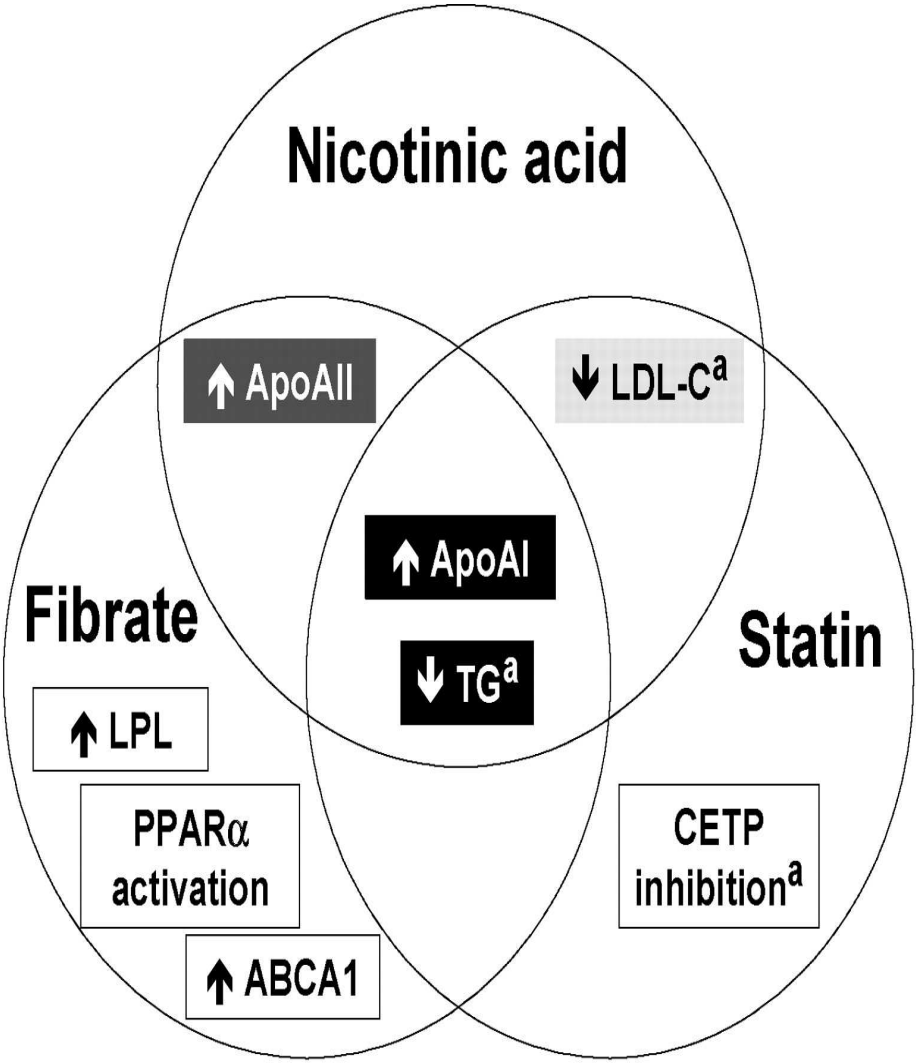
In the state of insulin resistance the LDL level is not affected much but the composition of LDL is altered in such a way it is small and more dense. This is because of increased triglyceride level. Increased triglyceride levels also leads to decreased HDL because cholesterol depleted HDL is more susceptible for destruction. In person with metabolic syndrome though fasting TG level is low, after food intake the transient rise of TGs can lead to the same process as above.

MANAGEMENT OF DYSLIPIDEMIA IN METS:

Niacin is of more significance in the treatment of most of the common abnormalities of lipids in metabolic syndrome. Niacin acts by decreasing lipolysis from adipose cells there by reducing the level of free fatty acid. This inturn leads to decreased availability of free fatty acids to liver. The binding of niacin to its receptor reduces cAMP which inturn inhibits lipolysis. However there is rebound elevation of FFA level. Niacin increases HDL level by ATP binding cassette AI- mediated transport of cholesterol.



Fibrates elevate HDL level by increased expression of Apo AI &II. The fibrates also has TG lowering action which is responsible for reducing LDL levels. Nowadays combination therapy is considered safe inspite of myopathy and rhabdomyolysis as a common adverse effect.



Mechanism expressed by:			
All agents shown	Nicotinic acid and fibrates	Nicotinic acid and statins	Fibrate or statin only

METABOLIC SYNDROME AND HYPERTENSION

Hypertension in metabolic syndrome is closely linked to dysfunction of vascular system which plays the key role in Mets. The classical pathway releasing NO is different from the pathway through which insulin releases NO. Insulin resistant state is favourable to vasoconstrictor tone. The adipose tissue present around the vascular system, through the secretion of adipokines alter the tone by its vasoactive property.

BLOOD PRESSURE CLASSIFICATION		
Blood Pressure Classification	**Systolic, mmHg**	**Diastolic, mmHg**
Normal	<120	*and* <80
Prehypertension	120–139	*or* 80–89
Stage 1 hypertension	140–159	*or* 90–99
Stage 2 hypertension	160	*or* 100
Isolated systolic hypertension	140	*and* <90

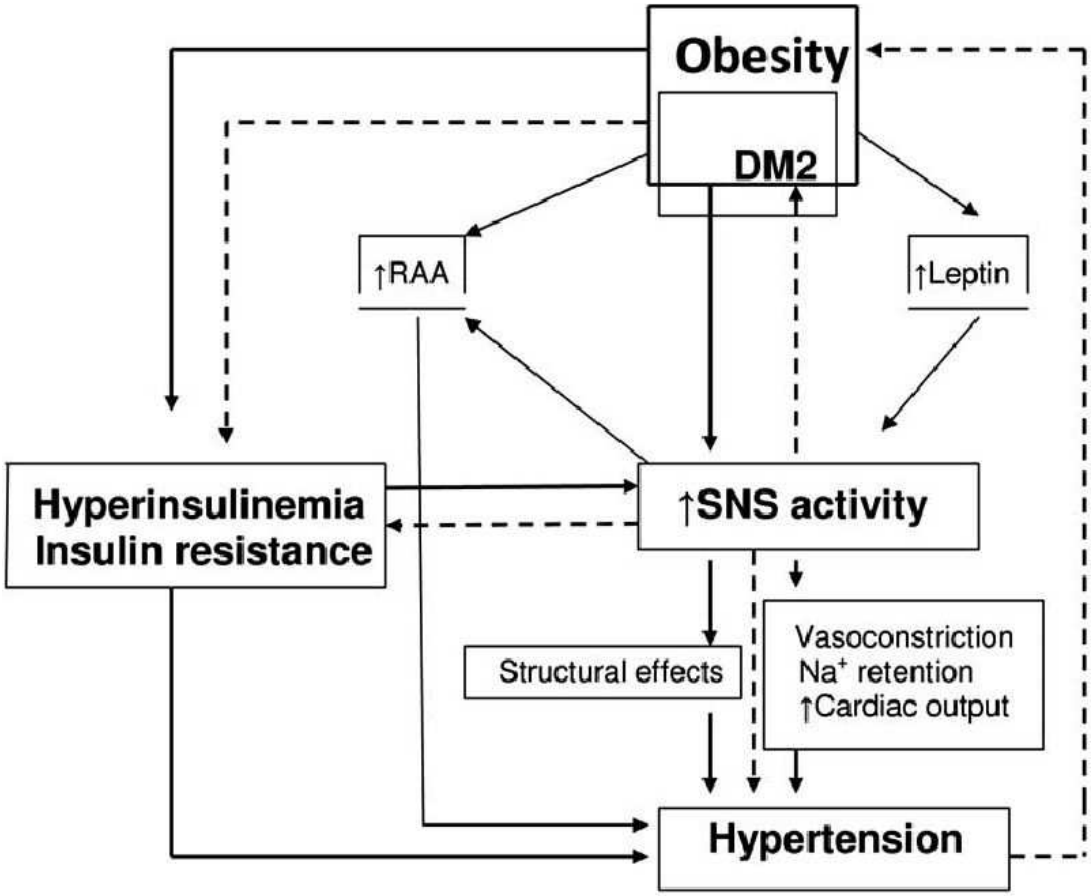
INTRODUCTION:

Since type2 DM has its effect more on vascular system, it is called as cardiometabolic syndrome. In 20th century, the physicians

identified that hypertension and diabetes occurred due to common mechanism[64]

ROLE OF SYMPATHETIC NERVOUS SYSTEM:

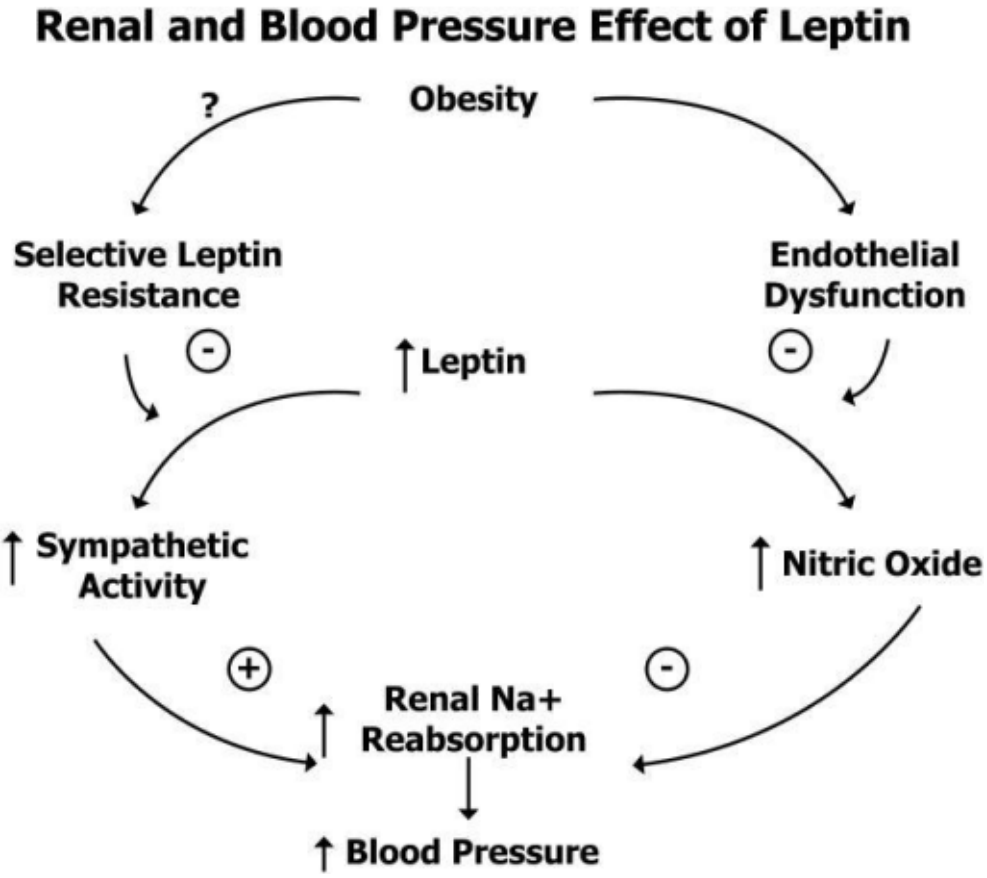
The increased levels of insulin, leptin and lipids cause exaggeration of sympathetic tone.



Among these hyper-insulinemia irrespective of changes in blood sugar level cause elevation of circulatory Nor-adrenaline. This is subsequently accompanied by elevation of blood pressure. Moreover this type of response to hyperinsulinema is centrally mediated as local infusion does not produce this response[65]. Increased insulin level also

favours sodium reabsorption predisposing to hypertension. Obese persons need more arterial pressure to maintain sodium homeostasis leading to impaired pressure natriuresis.(64)

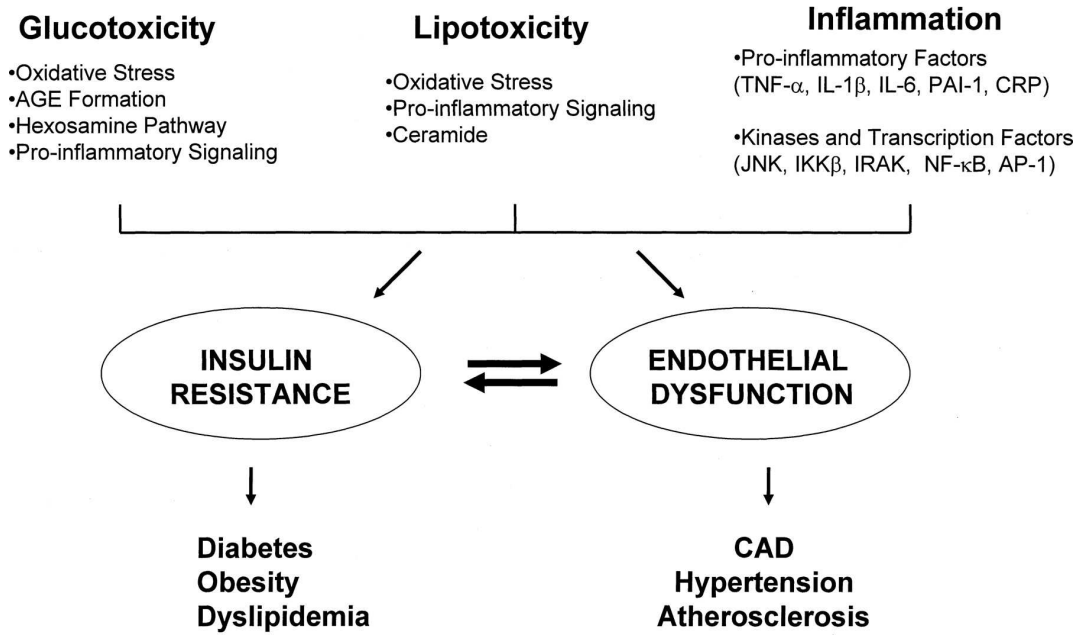
Leptin apart from its effect on appetite also activates sympathetic nervous system through the hypothalamus resulting in hypertension. This action is mediated through ventro , dorso medial nucleus of hypothalamus(66)



Finally higher levels of FFA in circulation of visceral obese patients leads to sympathetic system activation.

INSULIN RESISTANCE AND ENDOTHELIAL DYSFUNCTION

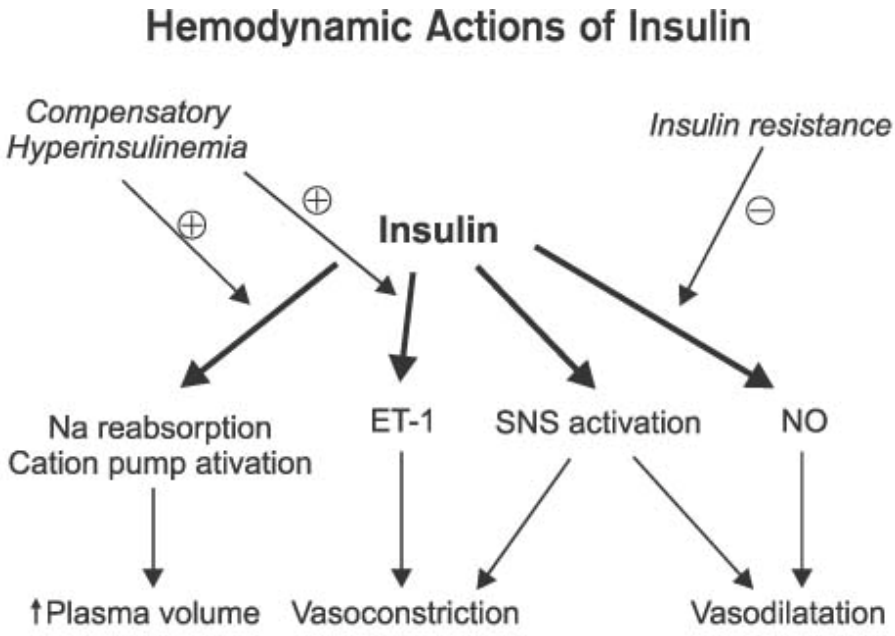
Himsworth's work in 1939 postulated that type II DM is insulin resistance state more than the deficiency of insulin. The mechanism through which insulin resistance causing dysfunction of endothelium is complex which involves inflammatory mediators from adipose tissue muscle and liver. The insulin resistance is in favour of endothelin -1 due to impairment of synthesis of NO leading to vasoconstriction



ROLE OF NO IN INSULIN RESISTANCE

In 1985 King identified the expression of insulin receptors in endothelial cells, as a physiological response insulin elicits NO mediated increase in flow of blood, through the capillary recruitment. Thereby insulin resistance leads to diminished NO synthase action. There is abnormality in basal action of NO mediated dilation [(67)]. Insulin induces

the release of NO synthase through a pathway different from the classical one which involves calcium dependent G protein coupled receptor like Ach receptor.



ROLE OF ENDOTHELIN -1 IN INSULIN RESISTANCE:

Oliver demonstrated the ability of insulin in stimulating endothelin-1 gene expression on the endothelium. There is alteration of levels of endothelin-1 in type 2 DM . Insulin has action on both NO mediated vasodilation and ET-1 mediateed vasoconstriction. Also endothelin -1 release leads to insulin resistance through the reduction of skeletal muscle blood supply and also decreases NO, increases oxidative stress thereby leading to pro-atherogenic state.

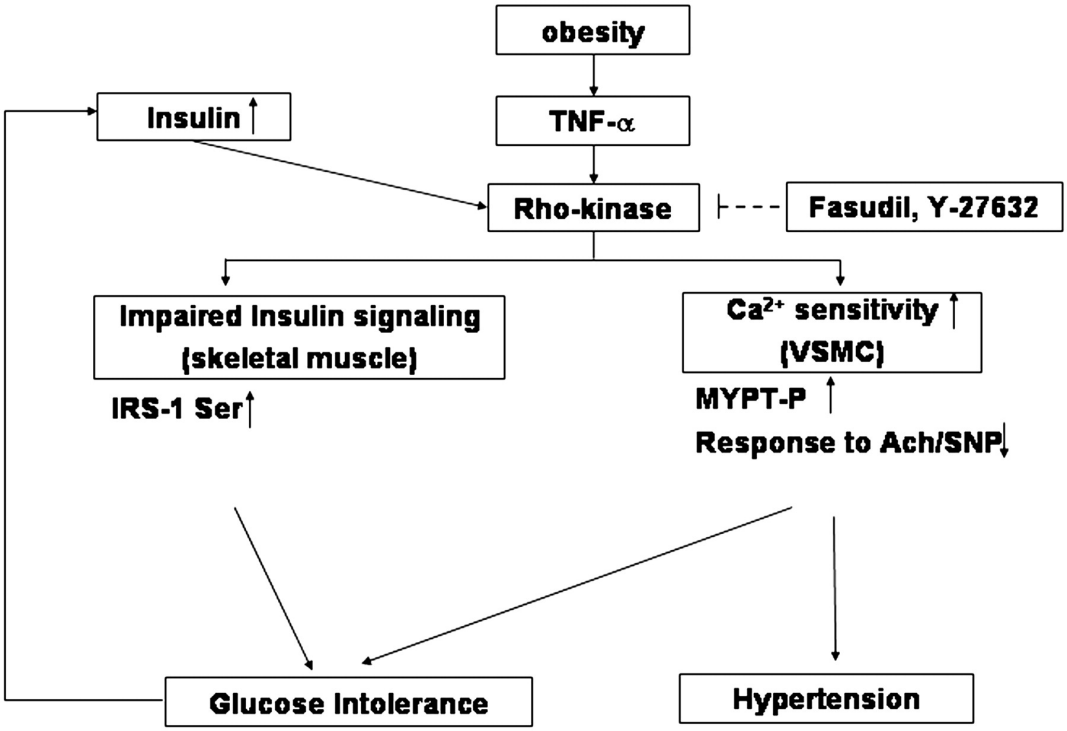
HYPERGLYCEMIA AND VASCULAR FUNCTION

Acute hyperglycemia in healthy individuals leads to impaired vasodilation both in micro and macro circulation. Insulin down regulates the stimulation of L-arginine transporter which also elevates NO and prostacyclin release in hyperglycaemic state which is unfavourable. The insulin mediated vasodilation doesnot occur in the presence of hyperglycemia added by vasoconstrictor effect of glucose per se.[68]

INSULIN ACTION ON BLOOD PRESSURE:

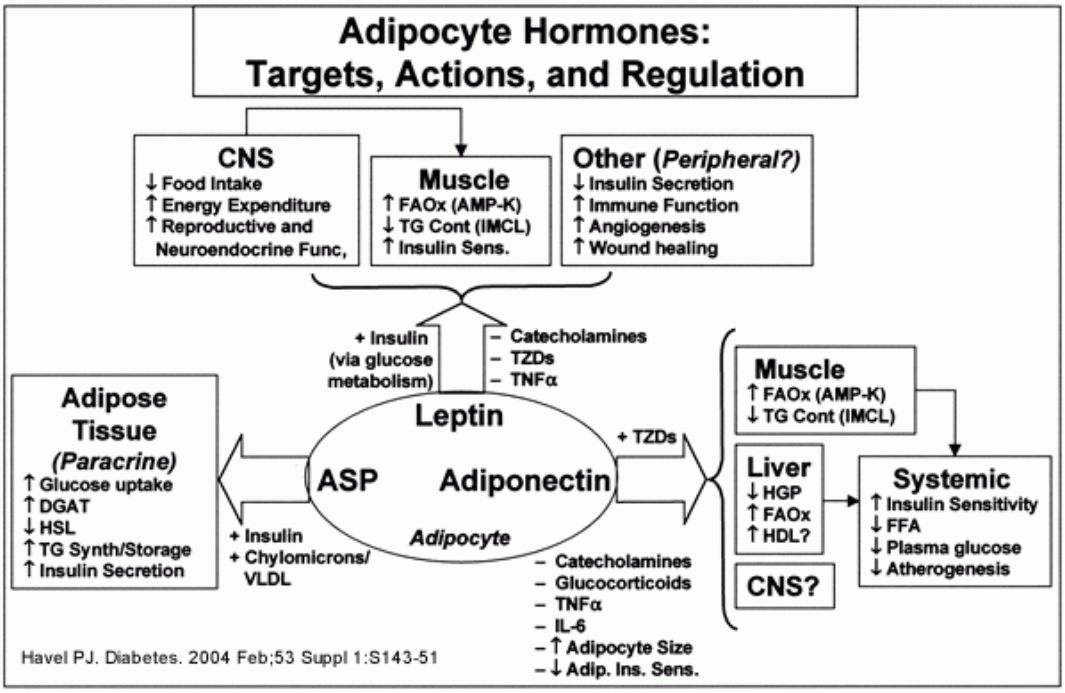
Insulin has both local and systemic effects on cardiovascular system. The systemic effect is that it affects renal and sympathetic nervous system. The insulin resistance resulting in compensatory hyperinsulinemia leads to increased reabsorption of sodium and sympathetic activity both of which results in hypertension. Individuals with primary hypertension who are lean also exhibits insulin resistance and hyperinsulinemia.

The drugs which are used in trestment of insulin resistance also has anti hypertensive action. For example, oral metformin used for the treatment of insulin resistance resulted in significant reduction in arterial pressure. One more example is the antihypertensive glitazone also improved insulin sensitivity.



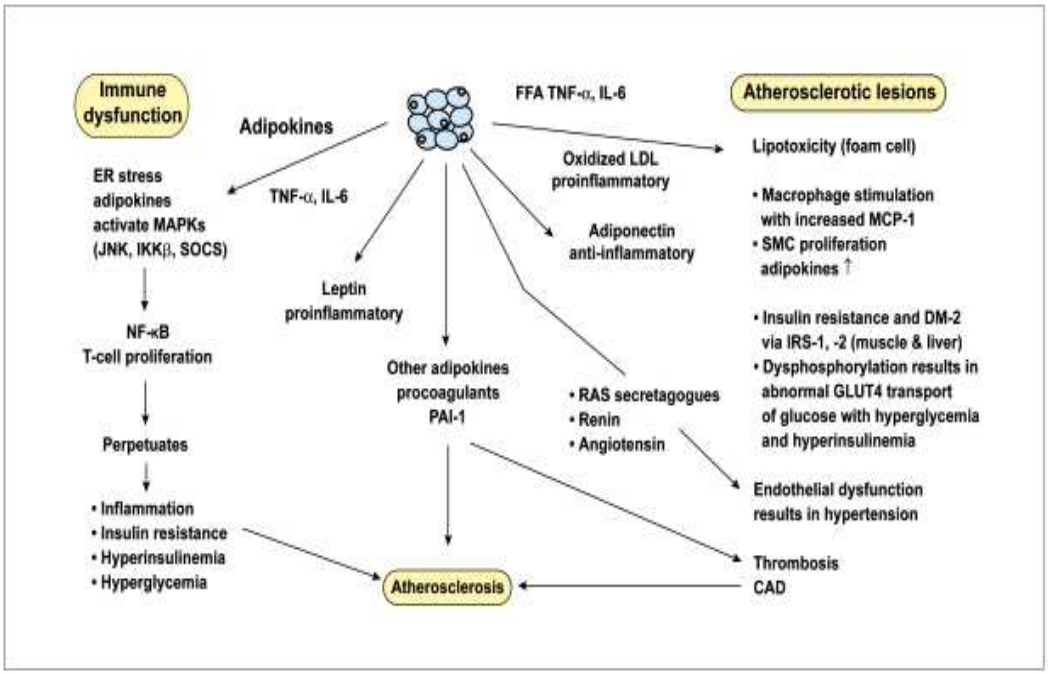
ROLE OF ADIPOKINES:

The adipocytes are reservoirs of energy that store in fed state and liberates FFA in fasting state. Apart from this adipocyte also does endocrine function of secreting adipokines the substance synthesised and released from adipocytes. Main source of inflammatory adipokines is the visceral fat accumulation which plays pivotal role in the development of cardiovascular disease and other disorders in the spectrum of metabolic syndrome.



PERIVASCULAR ADIPOSE TISSUE AND VASCULAR DYSFUNCTION

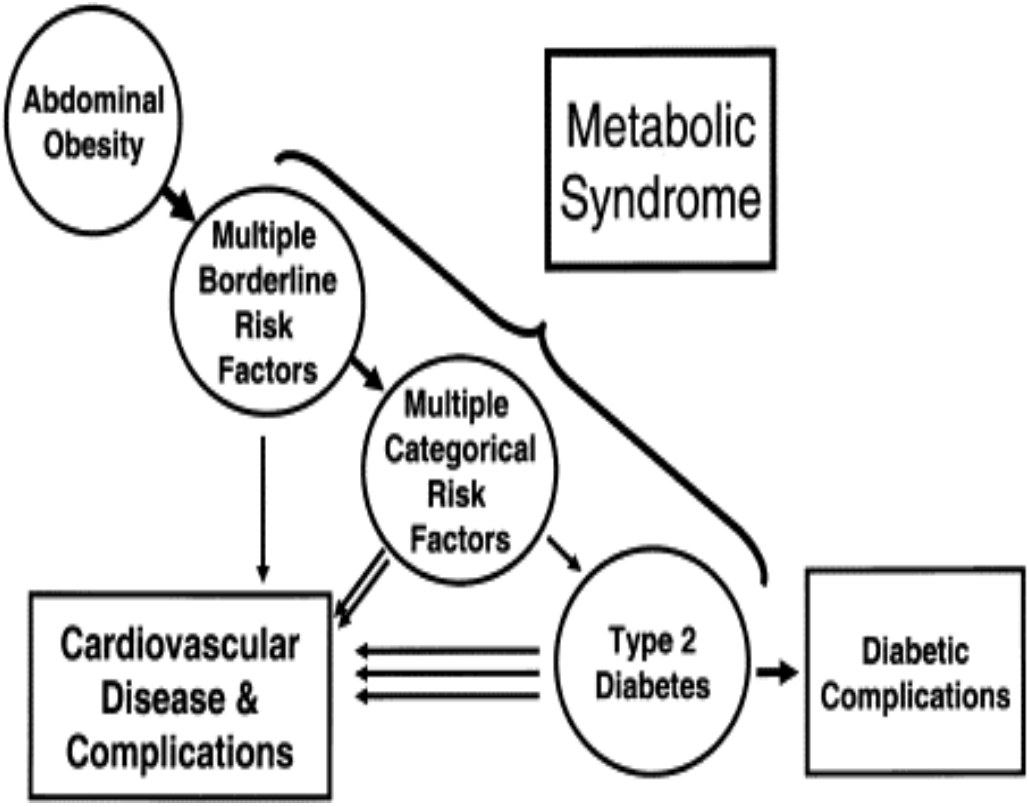
Adipose tissue as an endocrine organ has significant implication in knowing the pathophysiological relationship of fat and elevated blood pressure. Most of the arteries are surrounded by fat layer known as perivascular adipose tissue. Saltis described certain action of PVAT on contractility of vessels. PVAT promotes vasoconstriction when electrically stimulated [(69)] and due to reactive oxygen species produced by NADPH Oxidase which impairs endothelial function. The anticontractility of ADRF (ADVENTITIUM DERIVED RELAXING FACTOR) is through opening of K+ channels present in the smooth muscle of vessels.[(70)],


Immune dysfunction
Adipokines
FFA TNF-α, IL-6
Atherosclerotic lesions
Lipotoxicity (foam cell)
Oxidized LDL proinflammatory
ER stress adipokines activate MAPKs (JNK, IKKβ, SOCS)
TNF-α, IL-6
• Macrophage stimulation with increased MCP-1
• SMC proliferation adipokines ↑
Adiponectin anti-inflammatory
Leptin proinflammatory
NF-κB T-cell proliferation
• Insulin resistance and DM-2 via IRS-1, -2 (muscle & liver)
• Dysphosphorylation results in abnormal GLUT4 transport of glucose with hyperglycemia and hyperinsulinemia
Other adipokines procoagulants PAI-1
• RAS secretagogues
• Renin
• Angiotensin
Perpetuates
Endothelial dysfunction results in hypertension
• Inflammation
• Insulin resistance
• Hyperinsulinemia
• Hyperglycemia
Thrombosis
CAD
Atherosclerosis


NAFLD
Metabolic syndrome
▪ Abdominal obesity
▪ Hypertension
▪ Insulin resistance
▪ Hypertriglyceridaemia
▪ Small, dense LDL particles
▪ Low HDL cholesterol
▪ Glucose intolerance and/or diabetes
Chronic kidney diease
Increased uric acid
Increased total homocysteine
Hypovitaminosis D_3
Decreased adiponectin
Chronic inflammation (e.g. high levels of CRP and IL-6)
Hypercoagulability (e.g. high levels of fibrinogen and factor VIII)
Impaired fibrinolysis (e.g. high levels of PAI-1)
CVD

METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE

Inspite of uncertainities of link between obesity and coronary heart disease, AHA has observed obesity as risk factor for CHD. This is of significance in the prevention and management of coronary heart disease. 27th Bethesda conference identified obesity as class II risk factor that is the reduction of obesity leads to significant reduction in incidence of CHD. Though there is significant epidemiological evidence of correlation between obesity and heart disease the data based on clinical trials are not sufficient. Univariate analysis has observed linear relationship between obesity and CHD. But datas are less favourable in case of multivariate analysis.



MECHANISM OF RISK

The CHD risk is multifactorial and the risk factors can either be primary Eg LDL cholesterol or may be facilitatory like hypertension, smoking, obesity and type II Diabetes mellitus. The metabolic parameters associated with obesity contributing to cardiovascular disease risk are

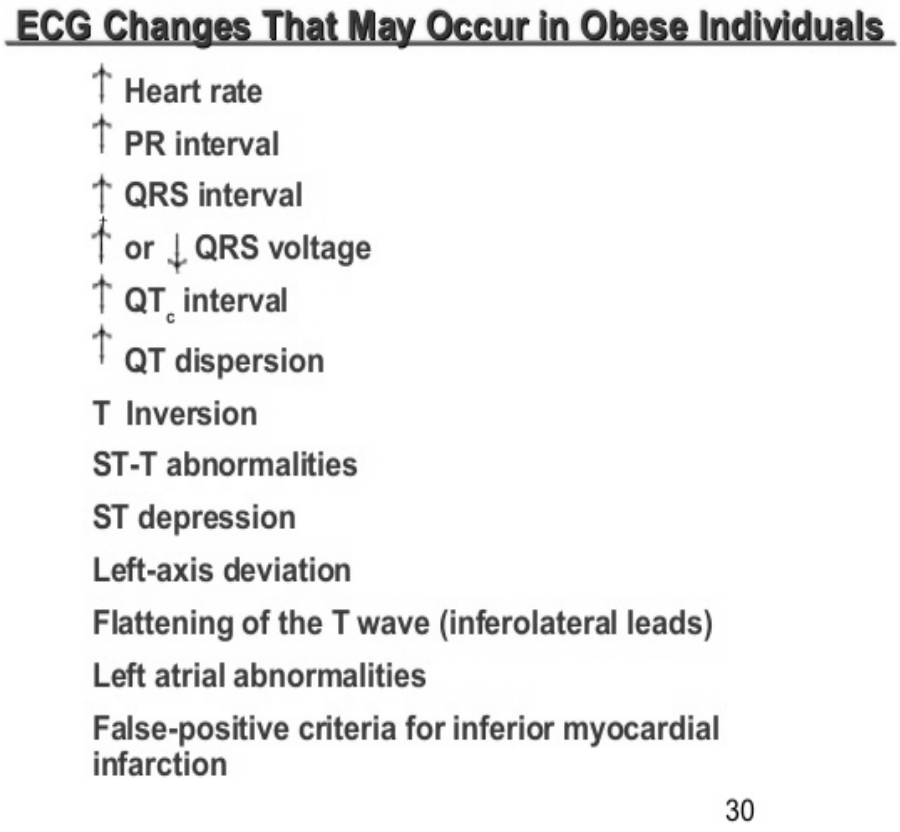
- Insulin resistance
- Type II Diabetes Mellitus
- Abnormal lipid profile
- Systolic and Diastolic Hypertension
- Sympathetic nervous system dysfunction
- Left ventricular hypertrophy
- Obstructive sleep apnoea

Persons having metabolic syndrome are at three fold higher risk of CVD. Obesity is associated with high end diastolic volume due to volume overload. This along with elevated blood pressure lead to LVH.The LVH is associated with increased risk of arrhythmia ,sudden cardiac death and heart failure.

HEART FAILURE AND OBESITY

There is also significant relationship between obesity and heart failure.The heart failure risk increased two folds with BMI>30Kg /m2 when compared with individuals who are not obese. The heart failure risk for men increased 5% and women increased 7%with each 1kg/m2 increase in BMI. The overweight women had increased risk but not in overweight men. But after developing heart failure the increased BMI lead to low rehospitalisation rates and decreased mortality.

ECG CHANGES IN OBESITY:



IDENTIFICATION OF PATIENTS AT RISK OF METABOLIC SYNDROME

The assessment of risk includes Blood Pressure, Waist circumference, Fasting glucose and lipid profile. The Endocrine society guidelines suggest evaluation every three years for people with one or more risk factors.(64).

Assessment of risk factor for CVD can be done using FRAMMINGHAM RISK SCORE.

The risk of type II DM is higher with persons having other components of Metabolic syndrome.

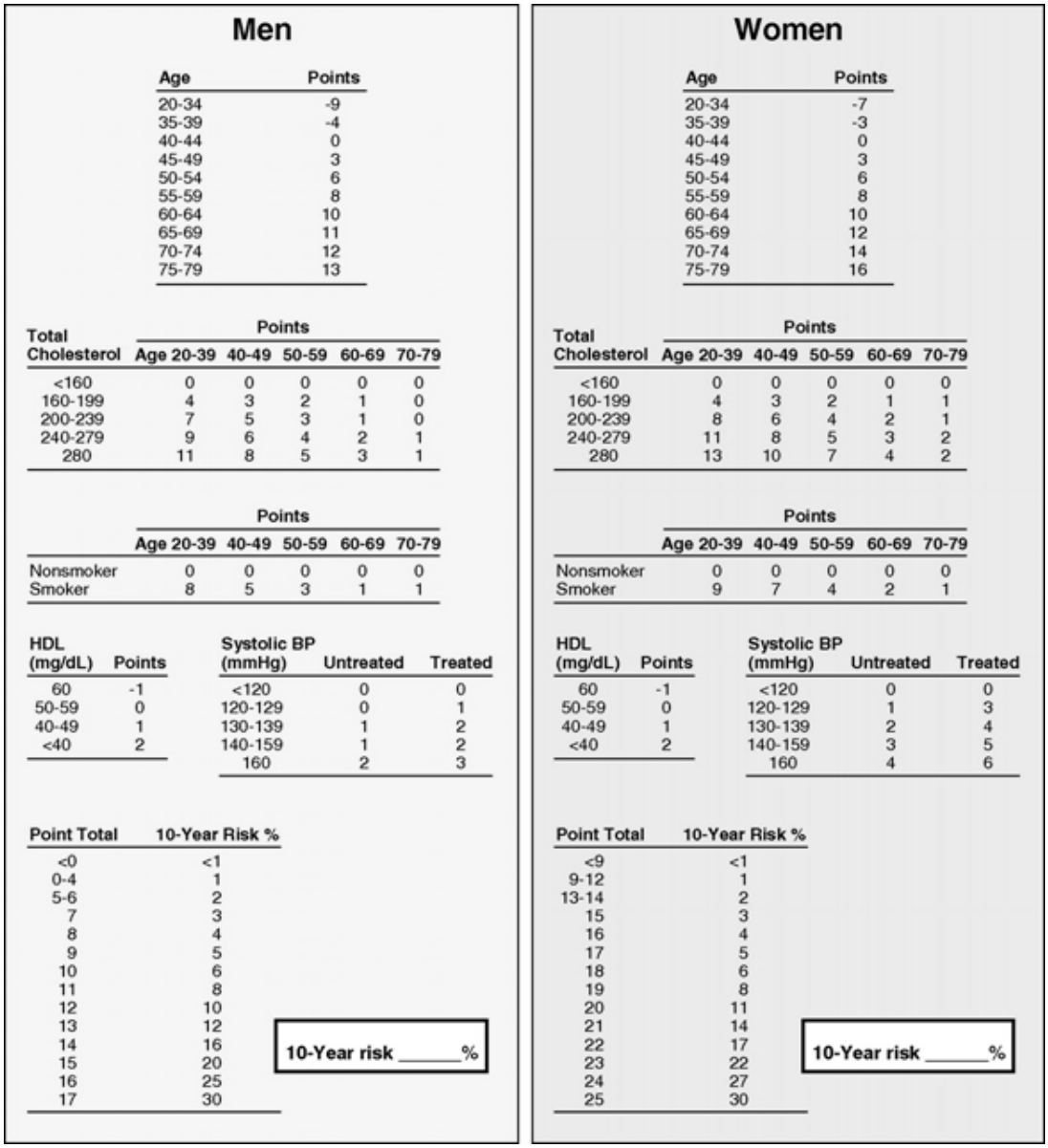
The risk of CVD in Metabolic syndrome is significantly related to Insulin resistance found in Metabolic syndrome than with obesity alone.CVD risk can be obtained by ECG, Carotid Doppler, Ankle Brachial blood pressure can be related to Metabolic syndrome.

Other disorders associated with Metabolic syndrome are Fatty Liver, Cirrhosis, CA Liver, Cholangio carcinoma, CKD, OSA, Hyperuricemia, gout Cognitive dysfunction to the extent of Dementia.

CLINICAL DIAGNOSIS OF METABOLIC SYNDROME

From clinical aspect Metabolic syndrome can be identified by simple criterias.

FRAMMINGHAM RISK SCORE:



Men

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points Age 20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
280	11	8	5	3	1

	Points Age 20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	Untreated	Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
160	2	3

Point Total	10-Year Risk %
<0	<1
0-4	1
5-6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
17	30

10-Year risk _____%

Women

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points Age 20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
280	13	10	7	4	2

	Points Age 20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	Untreated	Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
160	4	6

Point Total	10-Year Risk %
<9	<1
9-12	1
13-14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
25	30

10-Year risk _____%

RISK ASSESSMENT

Many studies have concluded that middle age group with metabolic syndrome are more at absolute risk of ASCVD in ten years. Even in young adults long term risk is high for ASCVD. The factor which is more contributing to increased ASCVD risk is premature diabetes mellitus.

In order to reduce the risk of ASCVD, persons with metabolic syndrome need long term management and follow up. The main aim is to decrease the risk factor. Individuals having ASCVD or Diabetes are in high risk state. People without ASCVD or Diabetes, risk is based on FRAMINGHAM RISK SCORE. This estimates CHD risk of 10 years.

TYPE II DIABETES MELLITUS

The existence of diabetes along with other risk factors favours higher risk which can be predicted by IFG or IGT. People with elevated IFG or I GT is termed as prediabetic state.IGT is more useful in uncovering the risk of development of Diabetes than IFG. So in order to decrease the need of OGTT, ADA decreased the threshold IGF from earlier 110 mg/dl to100mg/dl.So these individuals need lifestyle modification to delay the progression to TYPE II Diabetes mellitus.

MANAGEMENT OFUNDERLYING RISK FACTOR

Though many individuals are prone to metabolic syndrome they are not clinically manifested in the absence of obesity and sedentary lifestyle.

ABDOMINAL OBESITY

First priority in abdominal obesity and metabolic syndrome is weight reduction which can be achieved by

(i) Physical inactivity

(ii) Decreased calorie intake

(iii) Behaviour change

The achievement of weight loss is to 7 to 10%of baseline body weight in 6 to 12 months. This can be achieved by reducing calorie intake approximately 500 to 1000 calories per day.

Drugs for weight loss has limited utility in the management of obesity due to adverse effects. Bariatric surgery is increasingly indicated for severe obesity but has its own disadvantages.

PHYSICAL INACTIVITY

Increasing physical activity reduces the overall metabolic risk and more importantly ASCVD Risk. More than 30 minutes of brisk walking for 5 days preferably all days of the week. 60 mins of continuous or intermittent aerobic exercise can be done both for weight loss and its maintanence.

Avoiding sedentary leisure time activity also helps to achieve weight loss.

ATHEROGENIC AND DIABETOGENIC DIET

Diet low in cholesterol, saturated fatty acid, transfat, simple sugar, sodium with increased intake of whole grains, fruits and vegetables.

High levels of carbohydrate can increase dyslipidemia. 25 to 30% of total calories is provided by fat. If fat intake is more than35% it leads to elevated LDL-C. But if the fat intake goes less than 25% there is elevation of triglycerides and decrement of HDL-C.

Thus very low fat also worsen atherogenic lipidemia. Change in macronutrients can lead to weight reduction.

High protein, low carbohydrate diet decreases weight gain because high protein provides satiety than carbohydrate.

MANAGEMENT OF METABOLIC RISK FACTORS

ELEVATED BP

When only hypertension is present without CKD or diabetes the goal of BP is less than 140/100 .If CKD or Diabetes is present then BP goal is less than130/80.

Mild BP elevation can be dealt by weight reduction exercise, decreased sodium intake increased fresh fruit intake DASH Diet.

DASH Eating Plan Recomendations

Nutrient	Amount per Day[a]
Carbohydrate	55% of total calories
Total fat	27% of total calories
Saturated fat	6% of total calories
Protein	18% of total calories
Cholesterol	150 mg
Sodium	2,300 mg (1,500 mg)[b]
Potassium	4,700 mg
Calcium	1,250 mg
Magnesium	500 mg
Fiber	30 g

Antihypertensives are used to prevent long term adverse effects like stroke CKD, MI.

ELEVATED FASTING GLUCOSE

In patients with metabolic syndrome with IFG more than 100mg/dl weight reduction, exercise prevents onset of type II DM. Drug therapy

with metformin, Acarbose , Thiazolidanediones reduce the risk of type II DM.

PROTHROMBOTIC STATE

Individuals having metabolic syndrome have elevated fibrinogen, plasminogen activator inhibitor-1.

Drug therapy with LOW DOSE ASPIRIN is recommended in individuals with ASCVD and TypeII DM without ASCVD.

PROINFLAMMATORY STATE

Proinflammatory state is associated with metabolic syndrome where cytokines like TNF alpha, IL 6, fibrinogen, CRP are elevated.

In clinical practice CRP level is the simple way to assess proinflammatory state. Elevated levels of CRP can be reduced by weight reduction.

Drugs for treating metabolic syndrome are reported to reduce CRP. Example ACE inhibitors, statins, Thiazolidinediones.

MATERIALS

AND

METHODS

MATERIALS AND METHODS

Study Centre	Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai
Duration of the Study	6 months April 2015 to September 2015
Study Design	Cross-sectional study
Sample Size	100 (50-study group and 50-control group)
Inclusion Criteria	Patients with Hypothyroidism (study group) as diagnosed by 1. High TSH (> 10 m IU / ml) 2. Low FT4 (<0.93 ng/dl) Patients with euthyroidism (control group) as diagnosed by 1. Normal TSH (0.27- 4.2 m IU / ml) 2. Normal FT4 (0.93-1.7 ng/dl)
Exclusion Criteria	1. Patients with known hypothyroidism already on medication 2. Patients with hyperthyroidism and subclinical hyperthyroidism 3. Patients under treatment for any thyroid related disorder 4. Patients with liver disorder, renal disorder, congestive cardiac failure, pregnant women. 5. patients on OCP, statins and other medications that alter thyroid functions

IDF Criteria for metabolic syndrome	1. Central or abdominal obesity (measured by waist circumference :)in men > 102cms and in women >88 cms PLUS any two of the following four factors: 2. Triglycerides > or equal to 150 mg/dl 3. HDL Cholesterol: men < 40 mg/dl, women <50 mg/dl 4. Blood pressure > or equal to 130/ 85 mmHg or on anti-hypertensives 5. Fasting glucose > or equal to 100 mg/dl or on anti-diabetic drugs
Ethical committee approval	obtained
Data Collection and Methods	Patients are subjected to detailed history taking and clinical examination.
Consent	Written informed consent obtained
Methodology (Materials and Methods)	Patients newly diagnosed with hypothyroidism based on above said criteria are subjected to screening for metabolic syndrome
Product / Procedure / Investigation Details	1. Thyroid function tests 2. Fasting plasma glucose 3. Serum lipid profile 4. BP record 5. Anthropometric tests (height, weight, BMI , waist circumference)
Sponsorship (Yes/ No) If Yes details	No
Analysis plan	Analysis was done using SPSS Version 20. Significance was assumed with a p value of 0.05. Association between two categorical variables was done using chi square test. All p values were two tailed and significant when values were less than 0.05.
Conflict of interest	No

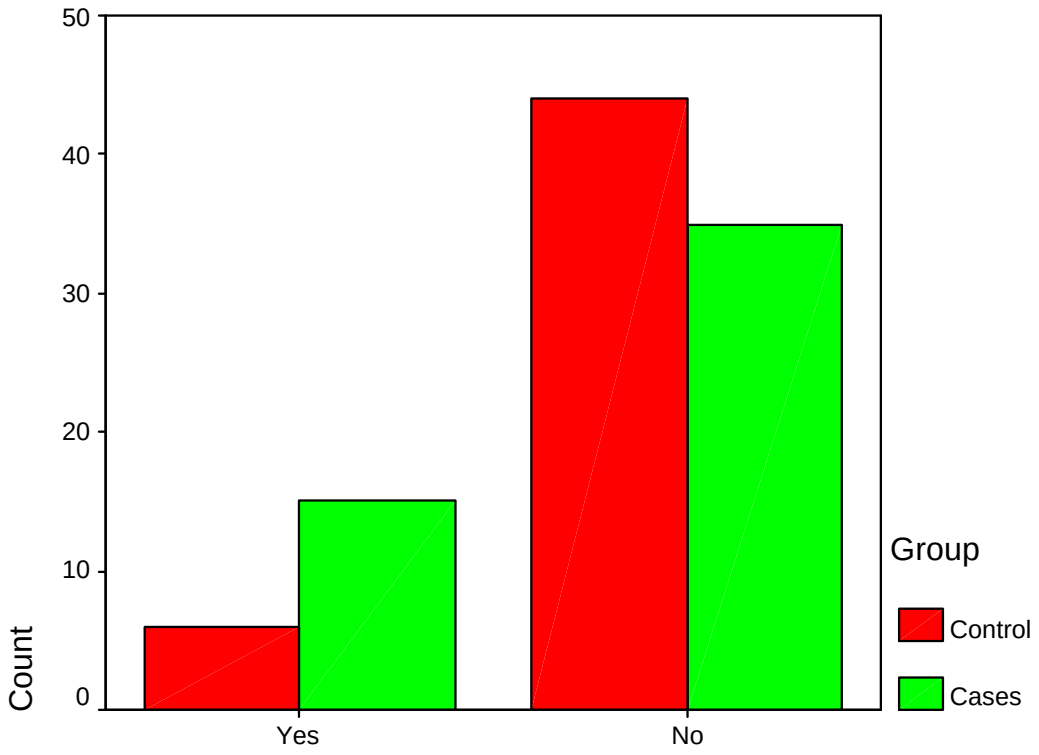
OBSERVATION

AND

RESULTS

OBSERVATION AND RESULTS

In our study comprising of 100 members, 50 belong to control group (euthyroid) and 50 belong to study group (hypothyroid). It is observed that 21 have metabolic syndrome in which 6 belong to control group and 15 belong to study group with distribution % of 28.6 and 71.4 respectively.



IDF CRIT.

There is significant correlation in the occurrence of metabolic syndrome between the control (euthyroid) and study (hypothyroid) groups, with p value of 0.048.

COMPARISON OF THE INCIDENCE OF METABOLIC SYNDROME IN HYPOTHYROID AND EUTHYROID GROUPS

			Group		Total
			Control	Cases	
IDF CRIT.	Yes	Count	6	15	21
		% within IDF CRIT.	28.6%	71.4%	100.0%
		% within Group	12.0%	30.0%	21.0%
	No	Count	44	35	79
		% within IDF CRIT.	55.7%	44.3%	100.0%
		% within Group	88.0%	70.0%	79.0%
Total		Count	50	50	100
		% within IDF CRIT.	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%

This table shows that the incidence of metabolic syndrome in the hypothyroid and euthyroid groups are 71.4 % and 28.6 % respectively, indicating that metabolic syndrome is more common among hypothyroid group

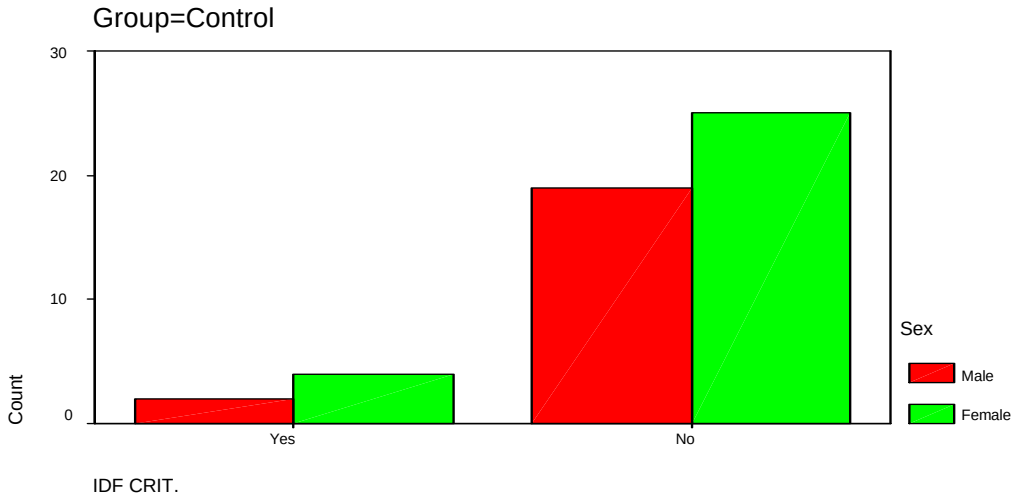
TABLE SHOWING CORRELATION OF INCIDENCE OF METABOLIC SYNDROME IN HYPOTHYROID AND EUTHYROID GROUPS

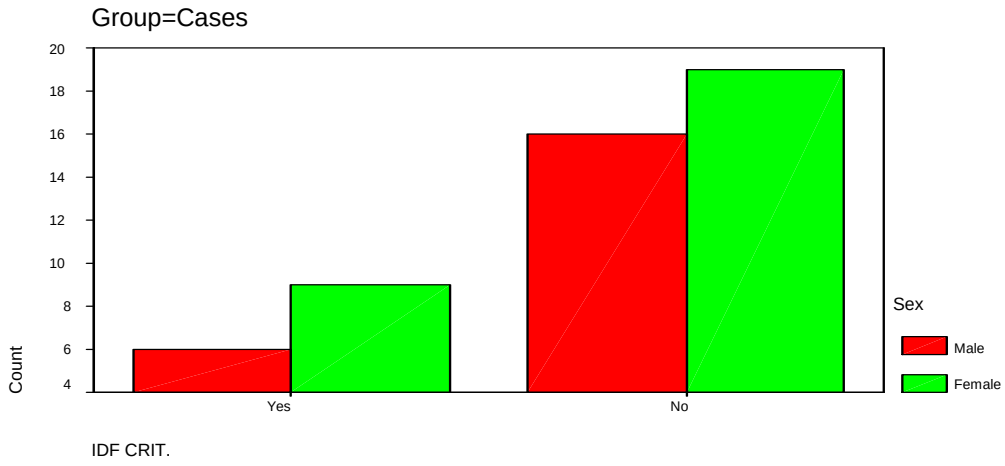
	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.882(b)	1	.027		
Continuity Correction(a)	3.858	1	.050		
Likelihood Ratio	5.012	1	.025		
Fisher's Exact Test				.048	.024
Linear-by-Linear Association	4.834	1	.028		
N of Valid Cases	100				

This table shows that the p value is significant , implying that there is a higher incidence of metabolic syndrome in hypothyroid patients.

SEX:

Among 21 members with metabolic syndrome 13 are female and 8 are male .In female 4 are from control group and 9 are from study group with 61.9% incidence found in female. Among male 2 are from control group and 6 from study group with 38.1% incidence in male.

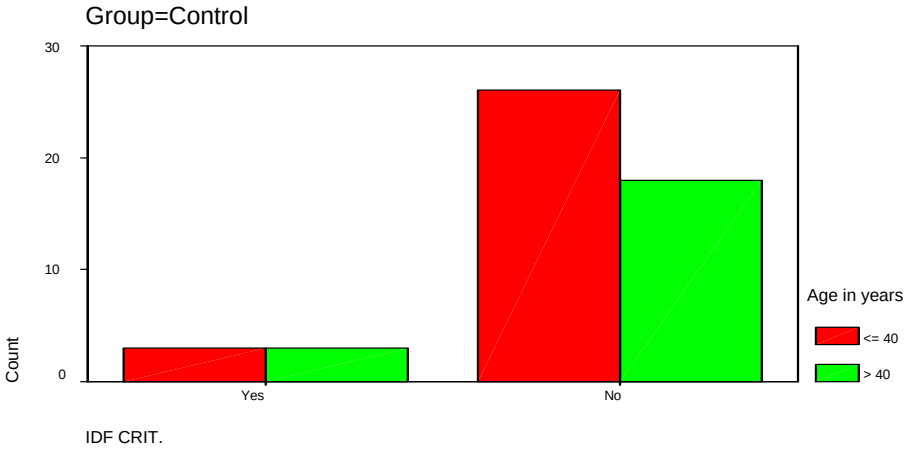


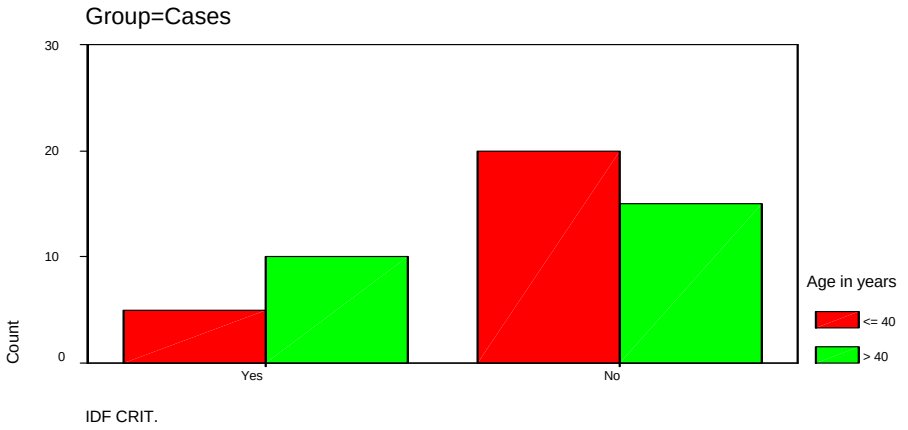


There is no significant correlation in the incidence of Mets between the control (euthyroid) and study (hypothyroid) groups in view of sex, with p value of 1.00 in control and 0.765 in study group.

AGE:

Among 21 members with metabolic syndrome ,13 are above the age of 40 and 8 are below the age of 40. In 13,about 10 are from study group and 3 are from control group with 61.9% distribution. Among those 8 members below age of 40, about 5 are from study group and 3 are from control group with distribution of 38.1%.

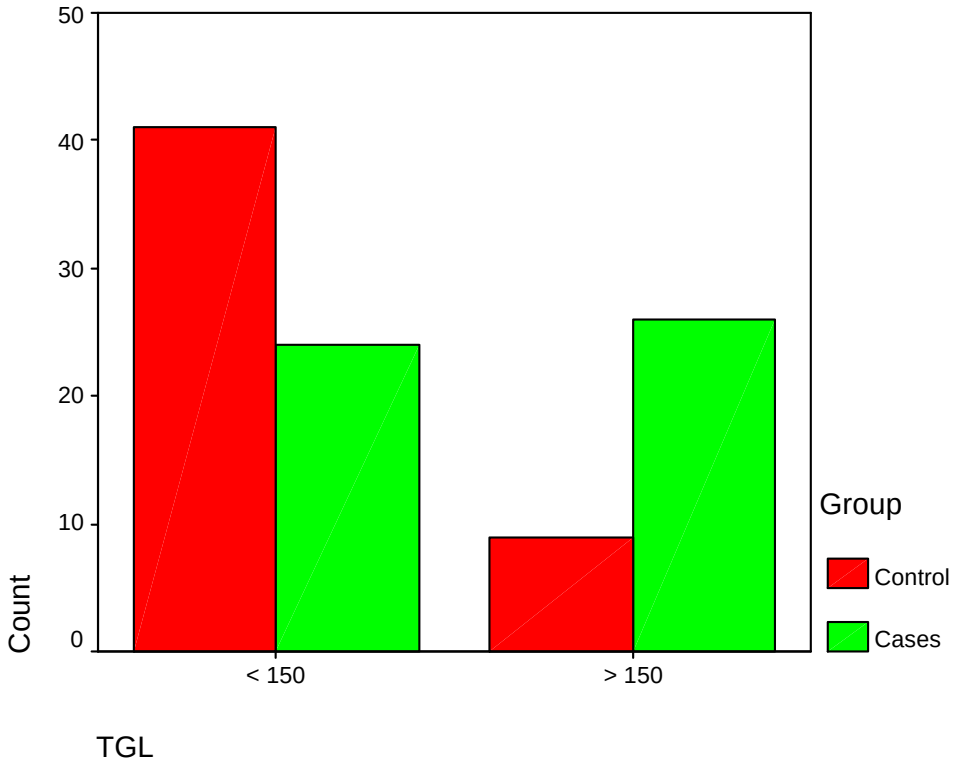




On the basis of age difference, there is no significant correlation between the control and study groups , with p value of 0.686 in control and 0.217 in study group for Mets

TGL:

Among 100 members ,65 have TGL less than 150 mg/dl. In these 65 members 24 belong to study group and 41 belong to control group with 36.9% and 63.1% respectively. Remaining 35 members have TGL more than 150mg/dl. Among these 26 belong to study group and 9 from control group with distribution of 74.3% and 25.7 %respectively.



In view of TGL values, correlation is significant between control and study group. P value is 0.001.

TABLE SHOWING THE DISTRIBUTION OF TRIGLYCERIDE LEVELS IN HYPOTHYROID AND EUTHYROID GROUPS

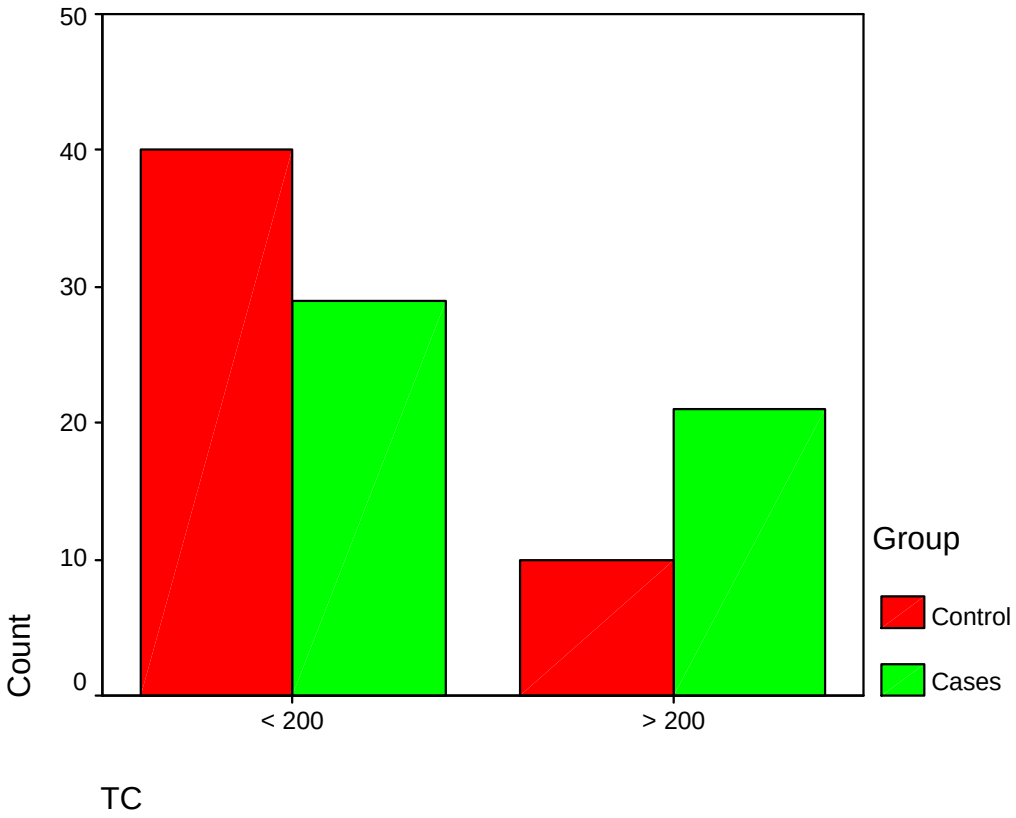
			Group		Total
			Control	Cases	
TGL	< 150 mg/ dl	Count	41	24	65
		% within TGL	63.1%	36.9%	100.0%
		% within Group	82.0%	48.0%	65.0%
	> 150 mg/ dl	Count	9	26	35
		% within TGL	25.7%	74.3%	100.0%
		% within Group	18.0%	52.0%	35.0%
Total		Count	50	50	100
		% within TGL	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%

This table shows that hypothyroid group has a higher percentage of cases with triglyceride levels more than 150 mg/dl when compared to euthyroid group. (74.3% Vs 25.7%)

TOTAL CHOLESTEROL:

Out of 100 members, total cholesterol is less than 200 in 69 members, in that 29 are from study group and 40 from control group with distribution of 42 %and 58 % respectively.

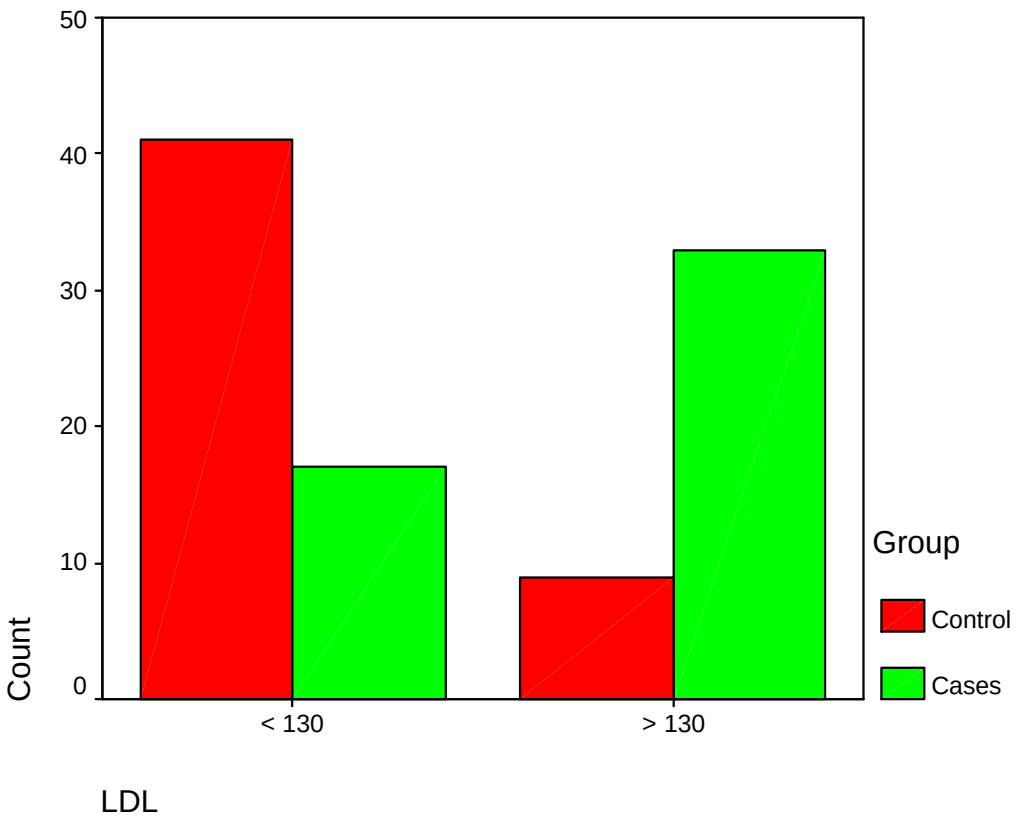
Out of 100, 31 members have total cholesterol more than 200. 21 of these are from control group and 10 are from study group with distribution of 67.7% and 32.3% respectively.



There exists significant correlation based on total cholesterol values between the study and control group. P value is 0.030.

LDL:

Among 100 members, 58 have LDL less than 130mg/dl with distribution of 29.3% in study group and70.7% in control group. Remaining 42 members have LDL more than 130mg/dl with distribution of 78.6% in study group and 21.4% in control group.

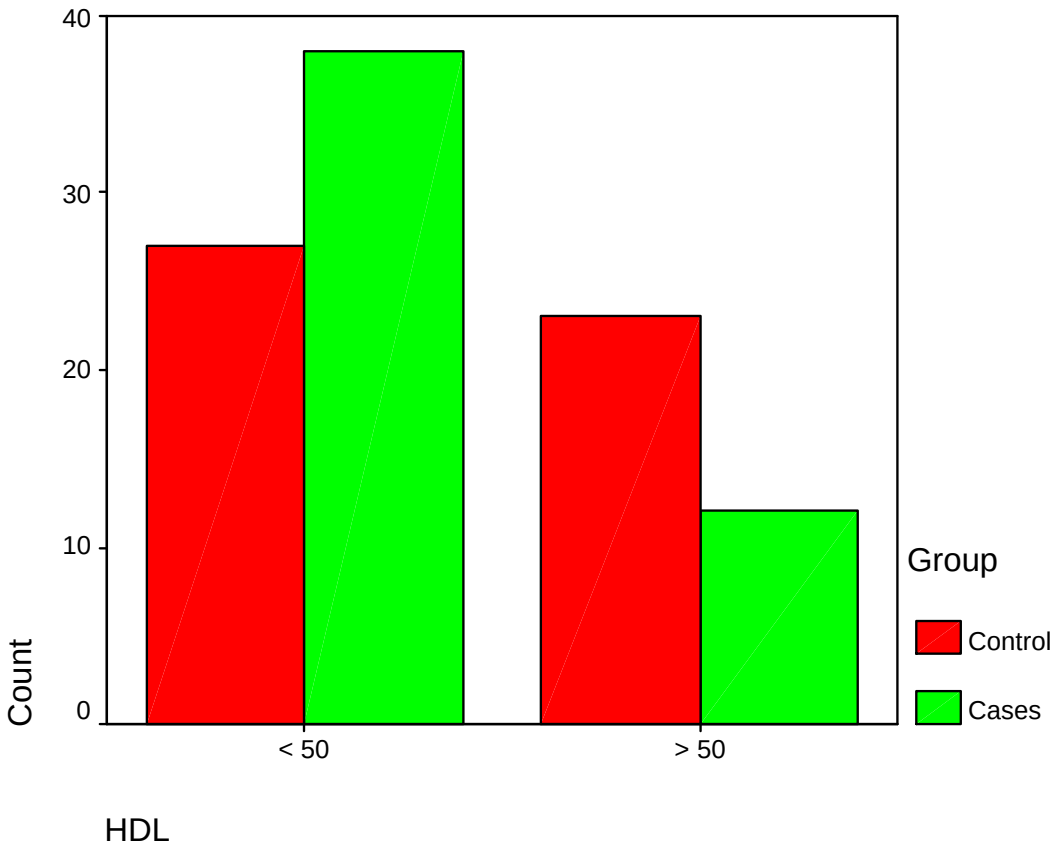


Correlation is found to be significant when LDL was compared between study and control group. P value <0.0001

HDL:

65 members out of 100 have HDL less than 50mg/dl. 35member have HDL more than 50mg/dl. Among these 65 members with HDL less than 50mg/dl,38 are from study and 27 are from control group with58.5% and 41.5% respectively.

Among 35 with HDL more than50mg/dl, 12 are from study with 34.3% and 23 are control with 65.7%.

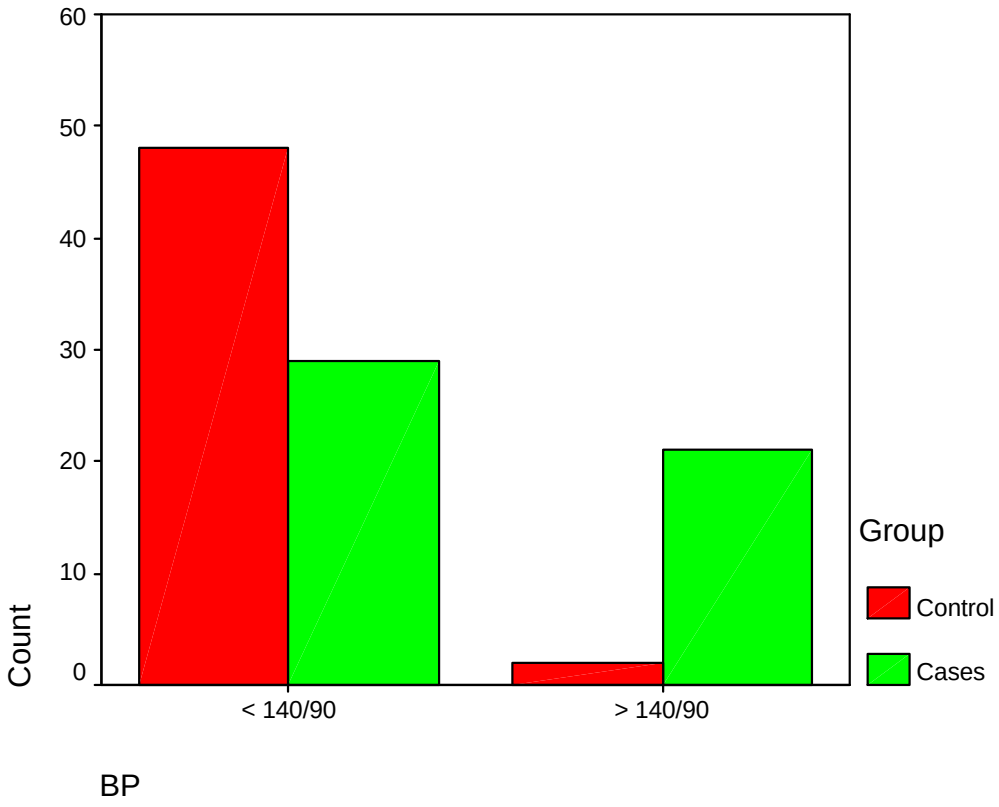


P value is 0.035 suggesting that correlation to be significant between the groups

BLOOD PRESSURE:

Out of 100 ,77 members have BP <140/90 mm Hg and 23 have BP >140/90 mmHg. Within that 77 people,29 are from study group and 48 are from control group with37.7% and 62.3%. respectively

Among those with BP>140/90 mm Hg, 21 are from study and 2 are from control group with distribution of 91.3% and 8.7% respectively.



Positive correlation is found between groups on basis of blood pressure with p value <0.0001

DISCUSSION

DISCUSSION

Hypothyroidism is present in about 3% of adult females .Increasing age is risk for hypothyroidism. Both Hypothyroidism and metabolic syndrome are associated with increased risk of CVD.

Thyroid hormone has significant role in various metabolic and developmental processes in our body. The effects of Thyroid hormones are stimulation of BMR, increased energy expenditure through increased ATP utility, and increased responsiveness through catecholamines by modulating adrenergic receptors. It also upregulates GLUT-4 in skeletal muscle and adipose tissue there by leading to lipolysis. Thus thyroid hormone has influence on lipid metabolism also.

Decreased thyroid level also leads to increase in TG's due to decreased activity of TG lipase from liver and there by reducing the clearance of TGs from plasma. There is significant overlap between CVS risk factors and effects of hypothyroidism like increased stiffness of arteries, elevated blood pressure, endothelial dysfunction and diastolic dysfunction.

The number of thyroid hormone receptors are decreased in persons with obesity. There is also association between insulin resistance and hypothyroidism both of which contributes to the development of metabolic syndrome.

Thus metabolic syndrome on the whole is the constellation of risk factors interrelated with risk factor or CVD, Type II DM, Hypercholesterolemia.

In Indian Journal 0f Endocrinology and Metabolism, The study conducted on "The Metabolic Syndrome in Thyroid Disease from Nigeria by Anthonia et al[71]. The study concluded that 1 in every 25 (i.e) 25% with Thyroid disorder have metabolic syndrome.

Our study also reveals that 30% of persons with thyroid disorder have metabolic syndrome.

The study on Age and Sex Differences in the clustering of metabolic syndrome factors by Jennifer L Kuk et al[72] concluded that incidence of metabolic syndrome increases with Age and also more common in Female.

In our study 61.9% of members with metabolic syndrome are above the age of 40 years and 38.1% are below 40 years. Also 61.9% of individuals with METs are female and 38.1% are male.

The study of ”Effects of Hypothyroidism as a cause of Hypertension” by Saito I, Ito K et al[73] concludes that in hypothyroidism 14.8% has BP>160/95 mm Hg compared toEuthyroid individuals in which 5.5% have BP<160/95mmHg.

In our study, among study group out of 50,21 have BP>140/90 mm Hg and in control group of 50 members ,2 have BP >140/90 mmHg.

The study of effects of thyroid disorder on lipid profile concludes that by Rizoz et al[74]. concludes that high TSH value increases total cholesterol, TGL, LDL nad decreases the HDL.

Two Chinese studies conducted on association between TSH level and total cholesterol by wang F et al[75], wanjia X et al[76] concluded that high TSH level independent of thyroid hormone level leads to elevated total cholesterol.

The Hunt[77] study, which is a population based study for association between TSH level and lipid profile arrived at significant (p for trend <0.001) linear increase in cholesterol, LDL, TGL levels with TSH levels and linear decrease (p for trend<0.001) in HDL cholesterolwith increase in TSH levels.

Our study also exhibits linear relationship between increase in TSH levels with increase in total cholesterol (p value 0.030), LDL (p vale <0.001), TGL (p value 0.001) and decrease in HDL (p value 0.035)

CONCLUSION

CONCLUSION

- Metabolic syndrome is more prevalent in Hypothyroid patients compared to Euthyroid individual

- Metabolic syndrome is more common in Female than Male as in hypothyroidism in which higher incidence is found in Female.

- Incidence of Metabolic syndrome increases with advancing Age.

- Thyroid stimulating hormone value in hypothyroidism has positive correlation with increase in Total cholesterol, Low Densty Lipoprotein and Triglycerides. It also has negatively correlation with HDL level.

- Hypothyroidism shows significant increase in Blood pressure compared to Euthyroid state.

- It suggests that there exists positive correlation between hypothyroidism and metabolic syndrome.

- Both Metabolic syndrome and Hypothyroidism increases the risk of Cardiovascular Disease. There is significant overlap in the pathogenesis and risk factors of Metabolic syndrome and Hypothyroidism.

- Early screening of Hypothyroidism in Metabolic syndrome and the vice versa, along with screening of other risk factors for Cardiovascular disease ,for early intervention will lead to significant reduction in Cardiovascular morbidity and mortality.

LIMITATIONS

LIMITATIONS

The presence and absence of confounding factors and diseases that influence the metabolic and thyroid parameters are not subjected for analysis in the study.

Sample included is limited involving 100 subjects.

BIBLIOGRAPHY

BIBILIOGRAPHY

1. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995;43:55-68.

2. Hollowell JG, Stehling NW, Flanders D, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87: 489-499.

3. Kratzsch J, Pulzer F. Thyroid gland development and defects. Best Pract Res Clin Endocrinol Metab. 2008;22:57-75.

4. spitzweg c, Heufelder AE, morris JC, thyroid iodine transport. Thyroid 2000:10:321

5. Arvan P, Di jeso B: thyroglobulin structure, function and biosynthesis.in:.the thyroid: fundamendal and clinical text, 9th, Braverman LE , utiger RD(Eds), Lippincott Williams and wilkins, philadelphia 2005.p.77

6. Vn herle AJ, Vassart G,Dumont JE. Control of thyroglobulin synthesis and secretion. (first of two parts). N E ngl J Med 1979:301:239

7. Moreno JC. Identification of novel genes involved in congenital hypothyroidism using serial analysis of gene expression. Horm Res 2003:60 suppl 3 :96

8. Weetman AP, McGregor AM, autoimmune throid disease: further developments in our understanding. Endocr Rev 1994:15:788.

9. Mariotti S, Caturegli P, Piccolo P , et al. Antithyroid peroxidise autoantibodies in thyroid disease. J Clin Endocrinol Metab 1990:71:661

10. Nordyke RA, Gilbert FL Jr, Miymoto LA, Fleury KA. The superiority of antimicrosomal over antithyroglobulin antibodies for deducting hashimoto thyroiditis, Arch Intern Med 1993:153:862

11. Boukis MA, Koutra DA, Souvatzoglou A, et al.thyroid hormone and immunological studie din endemic goitre. J Clin Endocrinol. Metab 1983:57:859

12. Fukata s, Kuma K, sugawara M. relationship between cigarette smoking and hypothyroidism in patients with hashimoto thyroiditis. J endocrinol invest 1996: 19:607

13. McDonnell ME, Braverman LE, Bernado J . Hypothyroidism due to ethionamide. N Engl J Med 2005:352:2757.

14. klein AH,Meltzer s, Kenny FM. Improved prognosis in congenital hypothyroidism treate before age 3 months. J Pediatr 1972:81:912

15. Dussault JH, Couloumbe P,Laberge C,et al. preliminary report on a mass screening programme for neonatal hypothyroidism. J Pediatr 1975:86:670

16. Eugene D djemil A, van vliet G, sexual dysmorphism of thyroid function in newborns with congenital hypothyroidism. J Clin Endocrinolo metab 2005:90:2696

17. Higuchi R, miyawaki M ,Kumagai T et al. central hypothyroidism in infants who were born to mothers with thyrotoxicosis before 32 weeks gestation 3 cases. Paediatrics 2005:115:e623

18. iseki M, shimizu M, oikawa T et al. subsequential serum measurements of thyrotropin binding inhibitor immunoglobulin G in transient familial neonatal hypothyroidism. Jclin endocrinol metab 1983:57:384

19. Pacud D, huot c, gattereau A, et al. outcome in three siblings with antibody mediated transient congenital hypothyroidism. J pediatr 1995:127:275

20. Bartalena L, bogazzi F, braverman LE, martino E. effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neuro development j.endocrinal invest 2001:24:116

21. cosman BC, schullinger JN, bell JJ,Regan JA. Hypothyroidism caused by topical povidone iodine in a newborn with omphalocele Jpediatr. Surg 1988:23:356

22. Rodesch F, camus M,ermans AM,et al. adverse effect of amniofetography on fetal thyroid function. Am j obstet gynecol 1976:126:723

23. oliveiri A, stazi MA, mastroiacovo P, et al. a population based study on the frequency of additional congenital malformations in infants with congenital hypothyroidism: data from Italian registry for congenital hypothyroidism 1991-1998 . J clin endocrinol metab 2002:87:557

24. seibner R, merlob P kaiserman I, sack J, congenital anomalies concomitant with persistent primary congenital hypothyroidism. Am J med genet 1992:44:57

25. Roberts HE, moore CA, fernhoff PM, et al. population study of congenital hypothyroidism and associated birth defects Atlanta 1979- 1992. Am J med genet 1997 :71:29

26. Al jurayyan NA, AL hebrish AS, EL –desouki ML, et al. congenital anomalies in infants with congenital hypothyroidism. Is it a coincidental or an associated finding ? Hum hered 1997 :47:33

27. kumar j. gordillo R, kaskel FJ, et al. increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism J. pediatr. 2009:154:263

28. Pratt DE, Kaberlein G, Dudkiewicz A, Karande V, Gleicher N. The association of antithyroid antibodies in euthyroid nonpregnant women with recurrent first trimester abortions in the next pregnancy. Fertil Steril. 1993;60:1001–5.

29. Mannisto T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, et al. Thyroid dysfunction and maternal morbidity. J Clin Endocrinol Metab. 2010;95:1084–94.

30. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. LT4 in autoimmune thyroid disease during pregnancy. J Clin Endocrinol Metab. 2006;91:2587–91.

31. Verges B. Clinical interest of PPARs ligands. Diabetes Metab. 2004;30:7–12.

32. Shirai K. Obesity as the core of the metabolic syndrome and the management of coronary heart disease. Curr Med Res Opin. 2004;20:295–304.

33. Evans RM, Barish GD, Wang YX. PPARs and the complex journey to obesity. Nat Med. 2004;10:355–361.

34. Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. Am J Med Sci. 2005;330:280–289.

35. Pan DA, Lillioja S, Kriketos AD, Milner MR, Baur LA, et al. Skeletal muscle triglyceride levels are inversely related to insulin action. Diabetes.1997;46:983–988.

36. Boden G, Chen X, Ruiz J, White JV, Rossetti L. Mechanisms of fatty acid-induced inhibition of glucose uptake. J Clin Invest. 1994;93:2438–2446.

37. Niswender KD, Baskin DG, Schwartz MW. Insulin and its evolving partnership with leptin in the hypothalamic control of energy homeostasis. Trends Endocrinol Metab. 2004;15:362–369.

38. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol. 2004; 24:29–33

39. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet. 1991;337:382–386.

40. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. New Engl J Med. 2003;348:1625–1638

41. Wang SN, Yeh YT, Yang SF, Chai CY, Lee KT. Potential role of leptin expression in hepatocellular carcinoma. J Clin Pathol. 2006; 59:930–934.

42. Calle EE, Kaaks S, Calle EE. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004;4:579–591

43. Brakenhielm E, Veitonmaki N, Cao R, Kihara S, Matsuzawa Y, et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase- mediated endothelial cell apoptosis. Proc Natl Acad Sci USA. 2004;101:2476–2481.

44. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. J Clin Endocrinol Metab. 2007;92: 255–263

45. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin: an adipokine with potent proinflammatory properties. J Immunol. 2005;174:5789–5795.

46. Schaffler A, Ehling A, Neumann E, Nerfarth H, Tarner I, et al. Adipocytokines in synovial fluid. JAMA. 2003;290:1709–1710.

47. Redinger RN, Small DM. Bile composition, bile salt metabolism and gallstones. Arch Intern Med. 1972;130:618–630.

48. Bergeron C, Boulet LP, Hamid Q. Obesity, allergy and immunology. J Allergy Clin Immunol. 2005;115:1102–1104.

49. Bugianesi E. Review article: Steatosis, the metabolic syndrome and cancer. Aliment Pharmacol Ther. 2005;22(suppl 2):40–43

50. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005;96:939–949.

51. Lau DCW, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: Molecular links between obesity and atherosclerosis. Am J Physiol Heart Circ Physiol. 2005;288:H2031–H2041.

52. Kahn CR, et al. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. N Engl J Med. 1976;294:739–745.

53. Olefsky J, Farquhar JW, Reaven G. Relationship between fasting plasma insulin level and resistance to insulin-mediated glucose

uptake in normal and diabetic subjects. Diabetes. 1973;22:507–513.

54. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988;37:1595–1607.

55. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. Annu Rev Med. 1993;44:121–131

56. McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism In the etiology of type 2 diabetes

57. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. Diabet Med. 1998:15;539-553.

58. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO Consultation. Part 1: diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization; 1999. Available at: http://whqlibdoc.who.int/hq/1999/WHO_N CD_NCS _9 9.2.pdf. Accessed December 12, 2003.

59. Stephens JM, Lee J, Pilch PF. Tumor necrosis factor-alpha-induced insulin resistance in 3T3-L1 adipocytes is accompanied by a loss of insulin receptor substrate-1 and GLUT4 expression without a loss of insulin receptor - mediated signal transduction. J Biol Chem.199

60. Sugita H, Fujimoto M, Yasukawa T, Shimizu N, Sugita M, Yasuhara S, Martyn JA, Kaneki M. Inducible nitric-oxide synthase and NO donor induce insulin receptor substrate-1 degradation in skeletal muscle cells. J Biol Chem. 2005;280:14203–11.7;272: 971–6.

61. Carvalho-Filho MA, Ueno M, Carvalheira JB, Velloso LA, Saad MJ. Targeted disruption of iNOS prevents LPS-induced S-nitrosation of IRbeta/IRS-1 and Akt and insulin resistance in muscle of mice. Am J Physiol Endocrinol Metab. 2006;291: E476–82.

62. Carvalho-Filho MA, et al. S-nitrosation of the insulin receptor, insulin receptor substrate 1, and protein kinase B/Akt: a novel mechanism of insulin resistance. Diabetes.2005;54:959–67

63. Xu H, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112:1821–1830

64. E.Kylin, “Hypertonie and zuckerkrankheit,” Zentralblatt für Innere Medizin, vol.42,pp.873–877, 1921. G. Marañón, “Über hypertonie and zuckerkrankheit,” Zentralblatt für Innere Medizin, vol. 43, pp.169–176, 1922.

65. G. Lembo, R. Napoli, B. Capaldo et al., “Abnormal sympathetic overactivity evoked by insulin in the skeletal muscle of patients with essential hypertension,” The Journal of Clinical Investigation, vol. 90, no. 1, pp. 24–29, 1992.

66. A. J. Marsh, M. A. P. Fontes, S. Killinger, D. B. Pawlak, J. W. Polson, and R. A. L. Dampney, “Cardiovascular responses evoked by leptin acting on neurons in the ventromedial and dorsomedial hypothalamus,” Hypertension, vol. 42, no. 4, pp. 488–493, 2003

67. A. Calver, J. Collier, and P. Vallance, “Inhibition and stimulation of nitric oxide synthesis in the human forearm arterial bed of patients with insulin-dependent diabetes,” The Journal of Clinical Investigation, vol. 90, no. 6, pp. 2548–2554, 1992.

68. C. Renaudin, E. Michoud, J. R. Rapin, M. Lagarde, and N. Wiernsperger, “Hyperglycaemia modifies the reaction of microvessels to insulin in rat skeletal muscle,” Diabetologia, vol. 41, no. 1, pp. 26–33, 1998

69. Y. J. Gao, K. Takemori, L. Y. Su et al., “Perivascular adipose tissue promotes vasoconstriction: the role of superoxide anion,” Cardiovascular Research, vol. 71, no. 2, pp. 363–373, 2006

70. M. Löhn, G. Dubrovska, B. Lauterbach, F. C. Luft, M. Gollasch, and A. M. Sharma, “Periadventitial fat releases a vascular relaxing factor,” The FASEB Journal, vol. 16, no. 9, pp. 1057–1063, 2002. S. Verlohren, G. Dubrovska, S. Y. Tsang et al “Modulation of vascular function by perivascular adipose tissue: the role of endothelium and hydrogen peroxide,” British Journal of Pharmacology, vol. 151, no. 3, pp. 323–331, 2007. Y. J. Gao, Z. H. Zeng, K. Teoh et al., “Perivascular adipose tissue modulates vascular function in the human internal thoracic artery,” Journal of Thoracic and Cardiovascular Surgery, vol. 130, no. 4, pp. 1130–1136,

71. In Indian Journal 0f Endocrinology and Metabolism, The study conducted on “The Metabolic Syndrome in Thyroid Disease from Nigeria by Anthonia et al.

72. The study on Age and Sex Differences in the clustering of metabolic syndrome factors by Jennifer L Kuk et al

73. The study of ”Effects of Hypothyroidism as a cause of Hypertension” by Saito I, Ito K et al

74. The study of effects of thyroid dysfunction on lipid profile concludes that by Rizos et al

75. The study on TSH levels within the reference range are associated with serum lipid profile independent of thyroid hormones by wang et al.

76. The study on High normal TSH levels is asoociated with an atherogenic lipid profile in euthyroid non smokers with newly diagnosed assymptomatic coronary heart disease by wanjia et al.

77. The study on the association between TSH within the reference range and serum lipid concentration in a population based study. The Hunt study Asrold bo, vattan ZJ, nilsen TI, bjrorot et al.

ANNEXURES

PROFORMA

"STUDY ON THE PREVALENCE OF METABOLIC SYNDROME IN THE NEWLY DIAGNOSED HYPOTHYROID PATIENTS"

Name: Age/Sex: Patient ID:

Address: Occupation:

CLINICAL DETAILS:

PAST HISTORY: if present ,duration and treatment details.

TYPE 2 DM	
SYSTEMIC HYPERTENSION	
DYSLIPIDEMIA	
CLD	
TUBERCULOSIS	
CKD	
CORONARY HEART DISEASE	
CEREBROVASCULAR ACCIDENT	

PERSONAL HISTORY:

H/o smoking

H/o alcohol

General physical examination: **Head to toe examination:**

Pallor –

Icterus –

Cyanosis –

Clubbing –

Generalized lymphadenopathy –

Pedal edema –

Height -

Weight –

BMI –

Waist ratio –

VITALS

PR –

BP –

Temperature –

SYSTEMIC EXAMINATION:

CVS:

RS:

ABDOMEN:

CNS:

INVESTIGATIONS:

THYROID PROFILE:

FREE T3

FREE T4

TSH

COMPLETE HEMOGRAM

HEMOGLOBIN –

TOTAL COUNT –

DIFFERENTIAL COUNT –

RBC COUNT –

PLATELETS –

RENAL FUNCTION

SERUM CREATININE –

BLOOD UREA

LIVER FUNCTION TESTS

TOTAL BILIRUBIN –

ENZYMES - OT - PT - ALP -

TOTAL PROTEIN -

SERUM ALBUMIN -

FASTING PLASMA GLUCOSE –

SERUM LIPID PROFILE –

TOTAL CHOLESTEROL –

LDL –

HDL –

TRIGLYCERIDES

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.P.MANIVANNAN,
Postgradaute M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.P.MANIVANNAN,

The Institutional Ethics Committee has considered your request and approved your study titled **"A study on the Prevalence of metabolic syndrome in the newly diagnosed Hypothyroid patients" No.09052015.**

The following members of Ethics Committee were present in the meeting held on 12.05.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	:Deputy hairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
7. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
8. Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
9. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

4/6/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

INFORMATION SHEET

We are conducting a **"STUDY ON THE PREVALENCE OF METABOLIC SYNDROME IN THE NEWLY DIAGNOSED HYPOTHYROID PATIENTS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to compare the prevalence of metabolic syndrome in newly diagnosed hypothyroid patients with that of euthyroid cases and to aid in early screening and prevent the complications of metabolic syndrome in hypothyroid patients.

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do certain tests which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date:

Place:

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு :

புதிதாக கண்டு பிடிக்கப்பட்ட தைராய்டு சுரப்பி குறை (**Hypothyroidism**) உள்ள நோயாளிகளிடம் அனுசேபப் பிணி (**Metabolic Syndrome**) எனும் நோயை கண்டறிதல் ஆய்வின் நோக்கமாகும்.

ஆய்வு நிலையம் : பொது மருத்துவத்துறை, மற்றும் நீரிழிவு மருத்துவதுறை
சென்னை மருத்துவக் கல்லூரி, சென்னை-3.

பங்கு பெறுபவர் பெயர் :

உள்நோயாளி எண் :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இந்த ஆராய்ச்சியில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இந்த ஆராய்ச்சியில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன் ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். ☐

இந்த அறுவை சிகிச்சை முறைகள் ஒப்புள்கொள்ளப்பட்ட முறைகள் என்பதையும் இதனால் உடலுக்கு எந்தவிதமான உபாதைகளும் இருக்காது என்பதை அறிந்துகொண்டு இந்த ஆய்வில் பங்குபெற முழு மனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் _____

_____

பங்கேற்பவரின் கையொப்பம் _____ இடம் _____ தேதி _____

இடது கை பெருவிரல் ரேகை

ஆய்வாளரின் பெயர் _____

ஆய்வாளரின் கையொப்பம் _____ இடம் _____ தேதி _____

PATIENT CONSENT FORM

Study Detail	:	**"STUDY ON THE PREVALENCE OF METABOLIC SYNDROME IN THE NEWLY DIAGNOSED HYPOTHYROID PATIENT"**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

e) I hereby consent to participate in this study. ❑

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required. ❑

Signature / thumb impression: Signature of Investigator

Patient's Name and Address: Study Investigator's Name:

ஆராய்ச்சியின் தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனையின் பொது மருத்துவம் மற்றும் நீரிழிவு மருத்துவத்துறையில் புதிதாக கண்டு பிடிக்கப்பட்ட தைராய்டு சுரப்பி குறை (Hypothyroidism) உள்ள நோயாளிகளிடம் அனுசேபப் பிணி (Metabolic Syndrome) எனும் இரத்த அழுத்தம், உடல் பருமன், உயர் இரத்த சர்க்கரை மற்றும் உயர் கொழுப்பு போன்றவை ஒருங்கே கொண்ட நோயை கண்டறியும் ஆய்வு நடைபெற்று வருகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதனால் தங்களது சிகிச்சையில் பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆய்வில் தங்களுக்கு மருத்துவபரிசோதனை மற்றும் இரத்தப் பரிசோதனை செய்யப்படும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ, அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதை தெரிவித்துக்கொள்கிறோம்.

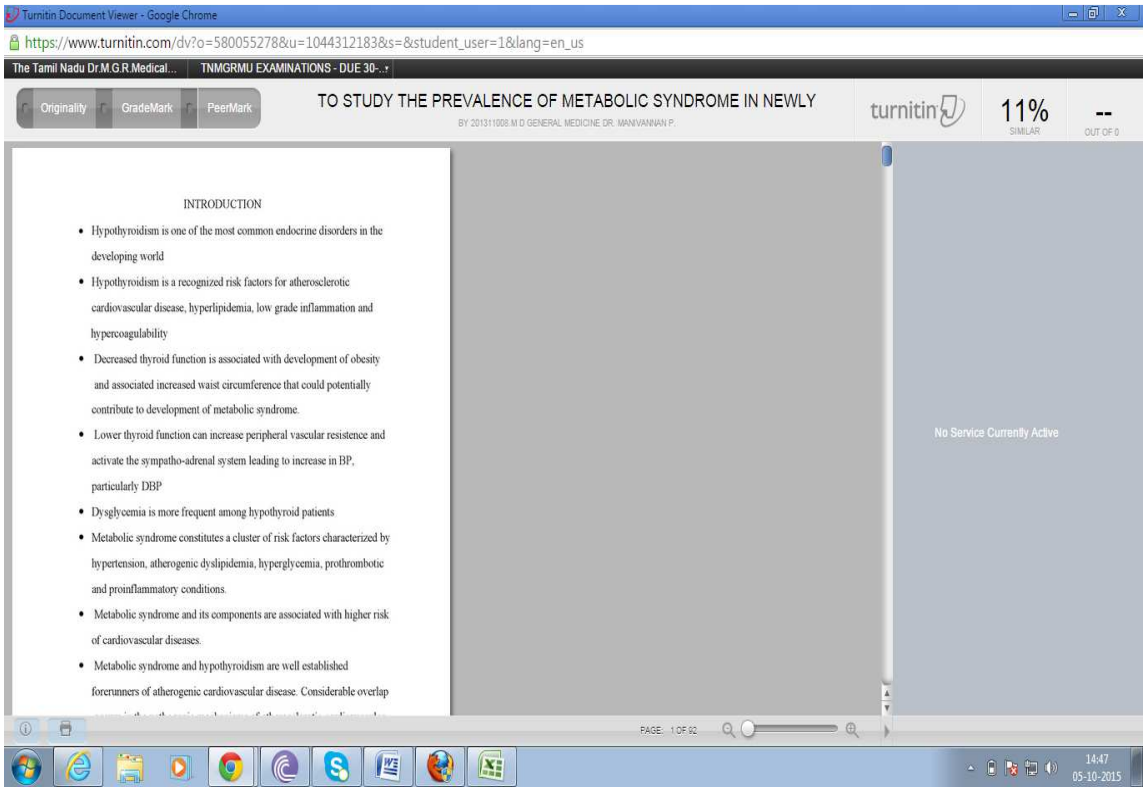
இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :

இடம் :

PLAGIARISM SCREEN SHOT



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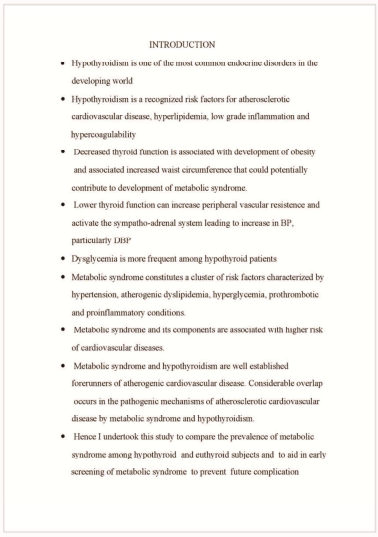

INTRODUCTION

- Hypothyroidism is one of the most common endocrine disorders in the developing world
- Hypothyroidism is a recognized risk factors for atherosclerotic cardiovascular disease, hyperlipidemia, low grade inflammation and hypercoagulability
- Decreased thyroid function is associated with development of obesity and associated increased waist circumference that could potentially contribute to development of metabolic syndrome.
- Lower thyroid function can increase peripheral vascular resistence and activate the sympatho-adrenal system leading to increase in BP, particularly DBP
- Dysglycemia is more frequent among hypothyroid patients
- Metabolic syndrome constitutes a cluster of risk factors characterized by hypertension, atherogenic dyslipidemia, hyperglycemia, prothrombotic and proinflammatory conditions.
- Metabolic syndrome and its components are associated with higher risk of cardiovascular diseases.
- Metabolic syndrome and hypothyroidism are well established forerunners of atherogenic cardiovascular disease. Considerable overlap occurs in the pathogenic mechanisms of atherosclerotic cardiovascular disease by metabolic syndrome and hypothyroidism.
- Hence I undertook this study to compare the prevalence of metabolic syndrome among hypothyroid and euthyroid subjects and to aid in early screening of metabolic syndrome to prevent future complication

MASTER CHART

CONTROL GROUP

SNO	AGE	SEX	TSH	FREE T4	W.C	T.C	TGL	HDL	LDL	BP	FBS	IDF CRIT.
1	13	F	3 .0	1.1	81	145	110	48	100	110/80	85	NO
2	21	F	0.4	1.6	89	158	131	56	98	120/70	100	NO
3	29	F	2.5	0.9	78	125	115	51	129	108/80	90	NO
4	18	F	1.9	1.1	83	190	119	39	115	120/72	107	NO
5	39	F	3.5	1.5	115	198	153	51	118	140/90	120	YES
6	28	F	4.1	1.1	79	123	132	48	110	110/82	105	NO
7	34	F	0.9	0.9	78	200	130	55	129	106/68	170	NO
8	26	F	3.5	1.3	89	119	110	43	100	120/80	93	NO
9	38	F	1.9	1.6	84	208	115	56	119	128/80	103	NO
10	23	F	0.8	1.5	110	148	134	51	128	124/74	81	NO
11	18	F	3.4	1.3	69	109	98	58	117	104/64	101	NO
12	39	F	2.7	1.7	79	150	109	59	129	100/80	105	NO
13	31	F	4.2	1.0	109	201	159	38	132	126/90	100	YES
14	28	F	0.5	1.6	88	168	139	48	100	130/72	99	NO
15	26	F	0.9	1.1	83	191	98	59	109	122/84	109	NO
16	34	F	3.4	1.7	91	120	210	51	126	124/70	99	NO
17	30	F	2.9	1.2	82	115	123	58	121	110/70	110	NO
18	40	F	4.1	1.5	78	148	125	50	99	108/86	106	NO

19	48	F	0.3	1.2	79	191	101	47	97	110/74	76	NO
20	51	F	3.8	0.9	80	115	100	38	118	132/80	120	NO
21	66	F	2.2	1.6	99	165	185	51	132	148/92	101	YES
22	70	F	0.7	1.2	90	185	130	56	160	132/80	91	NO
23	45	F	3.7	1.4	89	109	128	49	129	120/82	99	NO
24	50	F	1.8	1.6	85	210	85	50	126	110/72	117	NO
25	58	F	1.3	1.0	83	120	119	53	148	150/100	79	NO
26	47	F	2.8	1.5	79	98	145	43	117	132/80	78	NO
27	54	F	1.0	1.2	80	109	121	49	100	120/78	85	NO
28	61	F	3.6	1.4	105	260	171	36	139	140/90	80	YES
29	70	F	2.6	1.6	78	141	135	41	145	108/98	105	NO
30	17	M	1.1	1.0	75	136	137	49	109	136/70	78	NO
31	23	M	0.8	1.3	100	196	121	45	127	120/80	115	NO
32	31	M	3.5	1.5	80	208	148	53	119	134/92	120	NO
33	28	M	2.9	1.0	79	151	109	48	98	110/70	72	NO
34	21	M	1.2	0.9	78	175	132	46	100	120/70	100	NO
35	36	M	4.1	1.7	87	138	144	54	121	132/82	78	NO
36	39	M	4.0	1.1	110	169	164	53	195	130/80	135	YES
37	26	M	1.9	1.6	108	119	131	57	109	126/70	98	NO
38	25	M	2.4	1.7	78	108	148	68	119	120/82	96	NO

39	38	M	1.9	0.9	79	136	101	48	128	130/70	85	NO
40	40	M	3.2	1.4	80	148	140	48	110	122/86	110	NO
41	45	M	1.7	1.6	69	168	120	51	120	136/72	120	NO
42	51	M	3.9	1.1	71	220	131	50	121	136/84	110	NO
43	59	M	1.3	1.3	74	209	120	53	115	130/82	78	NO
44	61	M	0.9	1.6	80	110	99	48	151	126/74	98	NO
45	42	M	1.3	1.3	75	250	157	56	128	134/94	105	NO
46	68	M	1.6	1.7	71	270	175	48	108	120/92	123	NO
47	70	M	2.8	1.0	109	198	200	35	138	126/70	117	YES
48	59	M	4.2	1.2	72	151	111	45	119	130/84	88	NO
49	43	M	0.5	1.5	80	149	135	49	109	108/70	95	NO
50	62	M	0.9	1.3	91	290	128	53	121	130/108	105	NO

STUDY GROUP (HYPOTHYROID)

SNO	AGE	SEX	TSH	FREE T4	W.C	T.C	TGL	HDL	LDL	BP	FBS	IDF CRIT.
1	18	F	14.1	0.5	75	178	148	40	156	132/84	97	NO
2	29	F	12.6	0.3	81	210	145	39	140	134/98	70	NO
3	35	F	18.5	0.09	95	150	248	36	178	140/90	88	YES
4	37	F	25.1	0.03	90	185	131	42	191	96/62	85	NO
5	34	F	29.0	0.05	80	191	260	49	121	122/78	99	NO
6	34	F	18.1	0.3	78	138	128	51	127	110/82	81	NO
7	26	F	15.2	0.4	79	145	148	38	109	92/78	99	NO
8	29	F	30.1	0.07	90	268	198	46	138	140/94	110	YES
9	39	F	28.6	0.2	100	268	148	53	119	112/74	105	YES
10	28	F	35.2	0.08	85	218	178	54	181	106/60	99	NO
11	37	F	18.9	0.2	79	191	220	40	193	162/110	126	NO
12	31	F	15.0	0.4	80	178	195	56	161	140/94	115	NO
13	25	F	21.9	0.06	85	188	198	47	129	122/82	109	NO
14	40	F	45.3	0.2	80	319	115	58	121	120/70	105	NO
15	58	F	29.0	0.08	101	195	148	35	165	136/80	167	YES
16	51	F	60.1	0.3	79	298	131	55	161	180/118	98	NO
17	49	F	51.0	0.01	110	185	198	51	139	190/110	128	YES
18	71	F	28.3	0.1	85	265	230	53	210	160/108	88	NO
19	65	F	18.7	0.2	93	160	169	38	178	152/96	90	YES
20	62	F	12.5	0.3	102	151	145	53	128	186/102	98	NO
21	58	F	15.1	0.1	104	138	149	32	158	134/80	115	YES
22	45	F	25.0	0.7	80	278	158	57	199	120/70	109	NO
23	48	F	36.3	0.03	78	216	139	40	151	136/74	88	NO

24	63	F	40.1	0.6	95	178	159	51	168	134/80	115	YES
25	58	F	20.9	0.05	81	310	270	48	151	164/112	100	NO
26	49	F	15.8	0.1	85	215	120	48	120	130/86	99	NO
27	60	F	14.3	0.8	89	140	198	49	210	142/92	125	YES
28	62	F	98.1	0.3	83	240	134	46	198	120/80	89	NO
29	20	M	18.5	0.6	90	265	185	34	119	142/90	115	NO
30	28	M	40.0	0.09	97	178	119	40	197	130/82	125	NO
31	39	M	50.3	0.01	109	138	145	42	160	136/82	119	YES
32	31	M	82.3	0.2	85	230	133	41	178	142/80	89	NO
33	27	M	17.9	0.05	79	185	141	48	109	140/76	105	NO
34	29	M	12.0	0.7	91	191	220	43	98	126/82	101	NO
35	35	M	19.7	0.6	99	178	138	46	121	160/110	98	NO
36	38	M	21.3	0.2	111	180	290	51	210	164/110	150	YES
37	33	M	11.9	0.8	100	145	175	47	117	136/70	98	NO
38	38	M	15.3	0.4	95	218	198	49	197	140/84	105	NO
39	40	M	29.8	0.7	89	185	120	43	123	168/108	120	NO
40	51	M	71.4	0.5	108	138	210	48	195	132/90	210	YES
41	49	M	58.2	0.1	97	220	119	34	170	122/70	96	NO
42	60	M	34.9	0.3	101	278	178	41	127	160/112	170	NO
43	68	M	22.3	0.5	80	251	117	39	220	174/110	120	NO
44	49	M	19.0	0.2	89	210	195	41	97	200/120	105	NO
45	54	M	105.8	0.2	118	178	220	43	160	130/92	145	YES
46	58	M	20.1	0.8	108	193	121	48	148	120/80	95	NO
47	45	M	13.2	0.1	85	291	270	41	109	134/88	160	NO
48	65	M	17.1	0.7	119	148	139	50	198	168/102	138	YES
49	51	M	51.0	0.2	100	210	199	39	169	196/118	121	NO
50	59	M	42.8	0.3	107	165	188	34	139	152/110	138	YES

KEY TO MASTER CHART

S.NO.	-	Serial Number
TSH	-	Thyroid Stimulating Hormone
WC	-	Waist Circumference
TC	-	Total Cholesterol
TGL	-	Triglycerides
HDL	-	High Density Lipoprotein
LDL	-	Low Density Lipoprotein
BP	-	Blood Pressure
FBS	-	Fasting Blood Glucose
IDF CRIT	-	International Diabetes Federation
M	-	Male
F	-	Female